

Acquired human immunodeficiency virus/ HIV in the neonatal period

Vírus da imunodeficiência humana adquirida/HIV no período neonatal

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ABSTRACT

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Blocking mother-to-child transmission was one of the greatest victories against HIV infection. A reduction in infection rates down to below 2% was achieved by applying strategies such as the recognition of maternal infection (HIV serological testing or rapid test) during the prenatal period or at delivery, use of antiretrovirals, elective route of delivery according to the patient's viral load, and replacement of breastfeeding by formula. In Brazil, the recommended regimen includes the use of an anti-retroviral scheme composed of three anti-retroviral drugs from two different classes, from the 14th week of pregnancy (after the first trimester), in all pregnant women infected with HIV regardless of their virological or immunological parameters, use of intravenous zidovudine at the time of delivery, and of zidovudine in all children born to HIV infected mothers during the first four weeks of life. In special situations, adding other antiretrovirals, such as lamivudine and nevirapine, has been suggested. The benefits of maternal use of anti-retroviral drugs to prevent HIV transmission to children are unanimous. The safety of these short-term schemes has already been demonstrated, however, the association between maternal use of antiretrovirals drugs and congenital anomalies, prematurity, mitochondrial toxicity, anemia, neutropenia, and increased liver enzymes have been described. Serious effects rarely occur. Long-term follow-up of all children exposed to antiretroviral drugs is still necessary to answer many existing questions.

Key words: HIV Infections; HIV-1; Anti-Retroviral Agents.

RESUMO

O bloqueio da transmissão vertical foi uma das maiores vitórias contra a infecção pelo HIV. Houve redução das taxas de infecção a níveis inferiores a 2% com a aplicação de estratégias como reconhecimento da infecção materna (testagem sorológica anti-HIV ou teste rápido) durante o pré-natal ou no momento do parto, uso de antirretrovirais, via de parto eletiva de acordo com a carga viral e substituição do aleitamento materno pelo uso de fórmula láctea infantil. No Brasil, recomenda-se a utilização de esquema antirretroviral composto de três drogas antirretrovirais de duas classes diferentes a partir da 14ª semana de gestação (após o primeiro trimestre) para todas as gestantes infectadas pelo HIV, independentemente dos parâmetros imunológicos ou virológicos, uso de zidovudina por via venosa no momento do parto e de zidovudina para todas as crianças nascidas de mães infectadas pelo HIV, durante as primeiras quatro semanas de vida. Em situações especiais tem-se sugerido a adição de outros antirretrovirais, como a lamivudina e a nevirapina. Os benefícios do uso materno de drogas antirretrovirais para a prevenção da transmissão do HIV para seus filhos são unânimes. A segurança desses regimes em curto prazo já foi demonstrada, mas tem sido descrita associação do uso materno de drogas antirretrovirais e anomalias congênitas, prematuridade, toxicidade mitocondrial, anemia, neutropenia e aumento de enzimas hepáticas. Efeitos graves raramente ocorrem. Ainda é

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necessário acompanhamento em longo prazo de todas as crianças expostas aos antirretrovirais para responder muitas dúvidas existentes.

Palavras-chave: Infecções por HIV; HIV-1; Antirretrovirais.

INTRODUCTION

Blocking mother-to-child transmission was one of the greatest victories against HIV infection: reduced infection rates at levels of less than 2% was observed at the end of the 90's decade with the application of strategies such as maternal use of antiretrovirals (ARV), elective labor according to viral load, and replacing breastfeeding by infant milk formula.¹ Studies conducted in major cities in the Southeast of our country have confirmed the reduction of this transmission rate: 3.6% in Rio de Janeiro², 2.4% in São Paulo,³ and 3% in Belo Horizonte⁴.

METHODOLOGY

A non-systematic review of the literature was conducted in the Pubmed database, covering the past 10 years, using the terms HIV infection, HIV-1, antiretroviral, prophylaxis, and mother-to-child transmission.

REVIEW OF THE LITERATURE

Maternal-fetal transmission routes

The virus can be transmitted vertically in three moments: in the gestational period; in the peripartum period (during labor or birth); or in the postpartum period through breastfeeding. About 20 to 25% of infections occur during the intrauterine period by several mechanisms such as transplacental virus passage to fetal circulation or HIV infected maternal mononuclear cells when they directly reach fetal circulation or cell-to-cell infection of successive placental layers through contact at the intravillous space. It is estimated that 60 to 75% of transmissions occur during labor or birth. The transmission mechanisms include: breaks in the child's skin protection barriers with subsequent mucocutaneous exposure to blood and maternal contaminated secretions; ingestion of contaminated maternal fluids; transplacental micro-transfusions during labor, and rising viral infection.

Determinants of maternal-fetal HIV transmission

The risk of vertical HIV transmission is multifaceted, and thus, several intervention strategies during the gestational period have been studied with the aim to reduce the rates of maternal-fetal HIV transmission. The recognition of maternal social characteristics, as well as her health status, may indicate positive interventions for blocking transmission. It begins by the recognition of maternal infection through testing (HIV serology or quick test) during regular prenatal care or at childbirth.

The extended time of amniotic membrane⁵ rupture is associated with increased transmission and gradual increase in the rates of mother-to-child HIV transmission; this increase is associated with every elapsed hour from amniotic membrane ruptured. The role of the type of labor in reducing mother-to-child transmission has been an important topic of discussion.⁶⁻⁸ The surgical route can theoretically exert its protective role in several ways: by limiting the fetal exposure to contaminated maternal blood and vaginal secretions during his passage through the birth canal; by eliminating potential hazards such as vaginal instrumentation and episiotomy; by eliminating the risks associated with sexually transmitted diseases due to local inflammatory processes with consequent epithelial lesions in the vaginal mucosa and more significant site viremia; by preventing maternal-fetal micro-transfusions during uterine contractions during labor; and by decreasing the time of exposure to infected secretions after the rupture of amniotic membranes. However, the surgical intervention carries on risks that are inherent to surgical procedures. Thus, the elective surgical delivery is recommended for pregnant women in the 38th gestational week when plasma viremia is above 1,000 copies/mL or unknown in viral dosings after the 34th gestational week.⁹

One of the most consistent interventions has been the use of antiretrovirals by the mother and child. This strategy aims at better controlling the disease from the reduction in maternal plasma viremia and increased levels of T lymphocytes CD4⁺ and direct prophylactic action in the body of the child: through pre-exposure prophylaxis, when the anti-retroviral drugs cross the placental barrier, or post-exposure prophylaxis after birth, especially in those breastfed.

The ACTG076 study was one of the first to highlight the reduction in mother-to-child transmission among mothers who used prophylactic anti-retroviral treatment.¹⁰ In this double-blind, randomized, and

controlled placebo group study, women between 14 and 34 weeks of gestation were included, with LTCD4⁺ count > 200 cells/mm³, and who had no prior history of use of antiretroviral drugs. The experimental group was composed of mothers receiving zidovudine (ZDV) orally, in the prepartum period, intravenously in the peripartum, and their children receiving the drug orally, for six weeks after 24 hours after birth. The transmission rate was significantly lower in the group that received ZDV compared to the placebo group (transmission rate of 8.3% vs. 25.5%, respectively) showing a reduction in the transmission rate of approximately 67.5% (IC95%: 40.7-82.1). Since then, the use of ZDV during pregnancy has been recommended as a routine practice among pregnant women infected in developed countries, as well as in some developing countries such as Brazil.

After this milestone, several other studies have been conducted with ZDV prescribed in shorter periods of time or in combination with other medications; additionally, other anti-retroviral drugs were tested to evaluate the efficacy in blocking vertical transmission.^{11,12} The HIVNET012¹³ study evaluated the use of nevirapine (NVP) in one single dose given to mothers in labor, and to their children immediately after childbirth, and compared the group of women who received ZDV during labor and their children who received ZDV during the first week of life; this study demonstrated transmission rates significantly lower in the group with NVP (13.1% vs 25.1% in from the 14th to 16th weeks, p < 0.05).

Despite the practicality of the use of one antiretroviral single-dose, a later study¹⁴ showed the frequent appearance of viral isolates resistant to this medicine among women exposed to it (19% of women on the 6th the 8th postpartum week) and in their children (49% of children infected with HIV) highlighting the fragility of this long-term scheme.

Another multicenter study¹⁵ evaluated the addition of one single dose of NVP at childbirth and to newborns compared with placebo administration to pregnant women under antiretroviral triple therapy; significant difference in rates of HIV infection were not observed (1.4% vs. 1.6%, p = 0.82).

It is known that the higher the complexity of the anti-retroviral scheme defined as the combination of three antiretroviral drugs, the greater effectiveness in blocking HIV vertical transmission. The choice of antiretrovirals to compose the triple regimen and the best time during the pregnancy to start are described in Table 1. In Brazil, the use of the anti-retroviral scheme composed of three anti-retroviral drugs from two different classes starting on the 14th week of pregnancy (after the first trimester) in all HIV-infected pregnant women, regardless of their virological or immunological parameters is recommended⁹. The use of intravenous zidovudine at the time of delivery is also advocated.

All children born to HIV-infected mothers should receive ZDV at 4 mg/kg/dose every 12 hours during the first four weeks of life, as early as possible after birth, and ideally until the 48th hour of life.⁹

Table 1 - Antiviral recommendations by the STD and AIDS National Program for pregnant women HIV infected

Gestational period	Intervention
1 st trimester (<14 th gestational week)	Collect immunological (CD4 T-lymphocyte counts) and virologic (dosage of plasma viremia – viral load/CV) monitoring tests. ¹ If CD4 < 350 cells/mm ³ or symptoms of AIDS, diseases that alter the placental permeability – start antiretroviral triple scheme. Maintain anti-retroviral regimen postpartum. ² If CD4 > 350 cells/mm ³ or asymptomatic – wait for completion of the 1st trimester, interrupt antiretroviral
2 nd trimester (14 th to 28 th week)	Regardless of CD4 tests or CV: start triple antiretroviral scheme. - Preferred scheme: - ZDV + lamivudine/3TC + lopinavir/ritonavir Alternative schemes: - ZDV + lamivudine/3TC + nevirapine - ZDV + lamivudine/3TC + efavirenz
3 rd trimester (>28 th week)	Regardless of CD4 tests or CV: start triple antiretroviral scheme Preferred scheme: ZDV + lamivudine/3TC + lopinavir/ritonavir
Delivery	ZDV, via intravenous, initial dose 2 mg/kg in the first hour, followed by a maintenance dose of 1 mg/kg/hour until the clamping of umbilical cord. Start as early as possible, especially for those who had no opportunity of antiretroviral use during pregnancy. The use of zidovudine is independent of the type of labor planned, the use of anti-retroviral during pregnancy, and maternal history of ZDV resistance. If intravenous formulation is unavailable: ZDV 300 mg orally at admission/labor, followed by 300 mg every 3 hours, until the clamping of umbilical cord.

^{1,2} Recommendations applicable to all gestational periods.

However, in special situations, it has been suggested that adding other antiretrovirals could increase the chance of blocking mother-to-child transmission. Such situations are those in which the ideal control of maternal viremia at the time of delivery was not possible, when anti-retroviral drugs were not used during pregnancy or at childbirth, or the maternal viral load after the 34th week of pregnancy is unknown. In these situations, nevirapine has been added to the newborn regimen (in three doses: the first before the 48th hour of life, the second 48 hours after the first dose, and the third 96 hours after the second dose). The association with lamivudine in the first week of life has also been suggested, however, it has not yet become routine practice in Brazil.^{16, 17} For the children born to a mother with resistant viral isolates, the use of ZDV in conjunction with other anti-retroviral drugs should be discussed with specialists.

Besides the effectiveness in blocking the mother-to-child transmission, there are still many questions about the consequence of ARV regimens exposure to non-HIV-infected children. The safety of these regimens in the short term has already been demonstrated in clinical trials. The observation of the high incidence of congenital anomalies has been questioned in the population of children exposed to anti-retrovirals during pregnancy (1st semester), especially neural tube closure defects. The prevalence of birth defects per 100 born-alive to women with exposure to antiretroviral drugs in the first trimester of pregnancy was 2.9% (IC95%: 2.5-3.4) according to data from the elegant database of exposure registration in 22 years of study¹⁸, and it is similar to the prevalence reported in the American population.

The association between prematurity and maternal use of antiretroviral drug remains obscure. Some studies did not observe increase in risk, while others suggest an association between use of HAART and prematurity.^{19, 20} It should be noted that several other risk factors such as the use of licit and illicit drugs, co-infections, and lowered immunity may be present and increase the frequency of prematurity in this population, with increased morbidity among children vertically exposed to HIV.

Elevated incidence of mitochondrial toxicity has been observed, described as lactic acidosis, severe neurological manifestations, and transient cardiomyopathy in the French cohort²¹ with incidence of 0.26% at 18 months old (IC95%: 0.10 -0.54) among exposed

children compared to the incidence of 0.01% in the general population. However, such findings have not been confirmed in another cohort studies^{22, 23} and such association remains controversial.

In a prospective cohort of exposed infants in Latin America countries, including Brazil, Mussi-Pinhata et al. showed that about 60% of these infants presented some kind of non-HIV infection during the clinical laboratory monitoring for six months. In the multivariate analysis of that study, the factors associated with infection in the neonatal period were: maternal classification of HIV infection, smoking during pregnancy, anemia at birth, and number of people living in the same household.²⁴ In this same cohort, 20% of children (0.7-1.0/100 child-week) exhibited one episode of respiratory tract infection in the first six months of life. Bronchiolitis (81%) was the most common event with the frequent need of hospitalization (45.7%).²⁵

Other data show further occurrence of anemia and neutropenia, especially if associated with the use of anti-retroviral therapy combined.^{24, 26-28} Feitarna-Sperling et al.²⁸ obtained increased risk of anemia (OR 2.22, IC95: 1.06-4.64; p = 0.034) and neutropenia (OR 2.15, IC95%: 1.02-4.55; p = 0.045). Laboratory abnormalities such as increase in liver enzymes and anemia were observed between 63% and 24% of newborns at hospital discharge.²⁹ Lipshultz et al. also stressed that children exposed to antiretroviral drugs have compromised myocardium growth, however, with preserved function.³⁰

Anti-retroviral treatment

Studies revealed that during the first year of life, the risk of disease progression is high, and the introduction of early treatment is effective. Thus, in 2009, the Brazilian Consensus published as a recommendation the start of treatment in all under 12 months old, regardless of clinical symptoms, immunological classification, or viral load. In those over 12 months of age, it maintained its recommendation to start anti-retroviral treatment based on clinical and immunological criteria. The combined therapy with three antiretroviral drugs, including two classes of different drugs, is the initial treatment recommended for children and adolescents with HIV infection.³¹

DISCUSSION

The benefits of maternal use of antiretroviral drugs to prevent HIV transmission to their children are unanimous. However, potential adverse effects are expected; however, severe effects rarely occur.

The studies conducted to date are short-term. In this scenario, the long-term outpatient follow-up of all children exposed to antiretroviral drugs becomes essential with a periodicity of at least one year until new data are available (Table 2).

CONCLUSIONS

The blocking of maternal-fetal HIV transmission is possible from different interventions during pregnancy and in the neonatal period. There is a need for prospective follow-up of children born to HIV-infected mothers in order to measure long-term effects.

Table 2 - Antiviral recommendations by the STD and AIDS National Program for newborns to HIV infected women

Neonatal period	Intervention
Breastfeeding	Counter-indicated Initiate with formula and maintain ideally throughout the 1 st year of life. Crossed breastfeeding and use of maternal milk through home pasteurization are counter-indicated.
Laboratory follow up	CBC, AST, ALT, GGT, FA, glycaemia, serology for syphilis, toxoplasmosis, rubella, Cytomegalovirus, herpes simplex, HTLV/II, hepatitis B and C.
Antirretrovirals	Zidovudine - If > 35 weeks gestational age: 4 mg/kg/dose, at 12/12h VO or 3 mg/kg/dose at 12/12h EV, for four weeks. - If gestational age < 35 and > 30 weeks: 2 mg/kg/dose at 12/12h VO or 1.5 mg/kg/dose at 12/12h EV, for 14 days, increasing to 3 mg/kg/dose VO or 2.3 mg/kg/dose EV, from the 15 th day of life, held for a total of four weeks. - If < 30 weeks gestational age: 1.5 mg/kg/dose at 12/12h EV or 2 mg/kg/dose at 12/12h VO, held for a total of four weeks AZT Use by newborn is required, regardless of use or not by the mother during pregnancy or intravenous at childbirth. Risk factors indicating additional antiretroviral Nevirapine-additional oral doses ¹ - Birth Weight > 2,000 g: 12 mg/dose (1.2 mL) VO, in three doses ² - Birth Weight > 1,500 g and < 2,000 g: 08 mg/dose (8 mL) VO, in three doses ² - Birth Weight < 1,500 g: do not use nevirapine ¹ when the child cannot receive the medicine orally, in this case nevirapine should not be associated, even when indicated ² 1 st dose in the first 48 hours of life, 2 nd dose after 48 hours of the first dose, and 3 rd dose 96 hours after 2 nd dose. Lamivudine – in the first 2 weeks of life, in special situations, after discussing with specialists - 2 mg/kg/dose 12/12h VO for two weeks.

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