

Management of HIV During Pregnancy

Review Article

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Abstract

According to UNAIDS, in 2015, one hundred and fifty thousand children were infected by HIV worldwide, therefore the use of antiretroviral therapy (ART) during pregnancy is an important development for the reduction of maternal-fetal transmission. The treatment of a pregnant woman is done by combining two different ART classes. The combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with one non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) is generally recommended. The association of tenofovir/lamivudine (TDF/3TC) is the primary choice among the NRTIs, and zidovudine/lamivudine (AZT/3TC) is an alternative association although there is evidence showing that the use of AZT may be related to maternal and fetal anemia. Among the NNRTIs, the recommended drug is efavirenz, and nevirapine is the alternative drug. Treatment strategies with a PI drug must be associated with ritonavir so as to increase the serum levels of the drug and to therefore diminish the risk of viral resistance against the PI class. The main concern regarding the PI class is the increased risk of premature birth and low birth weight. The delivery method used depends on the viral load and the gestational age. When the maternal viral load is unknown or ≥ 1000 copies/ml, a C-section is recommended. When the viral load is undetectable or ≤ 1000 copies/ml, vaginal birth is a possibility. Elective C-section is often effective in preventing the vertical transmission of HIV in women who did not take ART during the pregnancy or in those who only took AZT.

Keywords: HIV Infection in Pregnancy; ART Drugs; Fetal Anemia; Prematurity; Delivery Route.

Introduction

In 2014, 36.9 million people lived with HIV and about 1.2 million people died due to conditions related to AIDS. These numbers keep increasing, often because of difficulties in accessing antiretroviral treatment (ART) [1]. Before June 2015, 15.8 million of the people infected by HIV were in treatment with ART. In 2014, approximately 73% of the 1.5 million pregnant HIV positive women received antiretroviral therapy for effective prevention of maternal-fetal transmission [2].

In Brazil, according to the Ministry of Health's (MH) data, before 2014 there were 757,042 registered cases of AIDS and the detection rates of HIV-positive pregnant women have increased significantly in the last 10 years. In 2004, there were 2.0 cases of HIV-infected pregnant women in every 1000 live births. This increased to 2.5 cases in every 1000 live births in 2013 [3].

When confronted with this reality, it is important to focus on the fact that the number of children exposed to HIV is increasing [4]. In 2015, according to the Joint United Nations Program on HIV/AIDS (UNAIDS), 150,000 babies were born infected with HIV.

In Brazil, it is known that for individuals 13 years of age and younger that are identified as HIV-positive, the main form of infection is maternal-fetal transmission [3]. According to the SENTINELA study, from 2000 to 2012 there were 69,500 notified cases of HIV-infected pregnant women. In 2011, the median rate of HIV detection in pregnant women in Brazil was 2.3 cases in 1000 live births, with a total of 6,540 notified cases. When compared with the national average, only the southern region of Brazil presented a higher detection rate. There it increases to 5.4 cases in every 1000 live births, and only the states of São Paulo and the Federal District showed a decrease in the detection rate

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of HIV-positive pregnant women, a trend that did not appear elsewhere in the country [5].

Vertical Transmission of HIV

The risk of HIV maternal transmission is higher than the risk of transmission by sexual contact, though the occurrence of the latter varies with the type of sexual practice. Only the risk of transmission by blood transfusion is greater than both, at a rate of 95 in 100 cases [6]. It is probable that more than 90% of the children living with HIV have been infected vertically [7].

It is not known exactly how HIV vertical transmission occurs, but it is believed that there are three main forms of transmission: during the intrauterine life, in the peripartum period and through breastfeeding. It is estimated that 25% of transmission cases occur during the gestational period, 75% during the peripartum period and each breastfeeding session increases the risk of transmission from 14% to 29% [8]. It is estimated that around 1000 children acquire HIV by vertical transmission daily. The establishment of ARV therapy reduces the number of children infected during the neonatal period from 15%-40% to less than 2% [9].

Brazilian, American and European HIV guidelines endorse the use of combined antiretroviral therapy including nucleosides, reverse transcriptase inhibitors and protease inhibitors [10]. The use of AZT monotherapy that was previously prescribed for pregnant women infected with HIV is not recommended anymore.

According to national guidelines, HIV-infected pregnant women have to receive antiretroviral therapy - preferably as a combination of three drugs from at least two different classes - regardless of viral load, immunologic status or clinical manifestations. The prescribed treatment for HIV-positive pregnant woman is the association of tenofovir/lamivudine (TDF/3TC), representatives of the NRTI class, combined with efavirenz, a NNRTI drug.

The association zidovudine/lamivudine (AZT/3TC) is the second choice among the NRTIs to be used as part of the initial antiretroviral therapy. In patients with anemia due to hematological toxicity - an adverse effect of AZT - it is not recommended to substitute enteric-coated didanosine (ddiEC) or stavudine (d4T) combined with lamivudine, since these are prohibited during pregnancy due to fetal lactic acidosis. The American guidelines do not recommend the use of abacavir/lamivudine (ABC/3TC) in patients with a viral load above 100,000 pre-treatment, preferring treatment with tenofovir/emtricitabine (TDF/FTC) or zidovudine/lamivudine (AZT/3TC) [10].

Regarding the NNRTIs, nevirapine (NVP) is the alternative drug to efavirenz. However it must be used carefully in patients with a count of LT-CD4+ >250 cels/mm³ due to the hepatotoxicity risk [11]. According to the American and Brazilian guidelines, use of efavirenz can be continued for patients who are already using the drug and have initiated pre-natal care in the first trimester. The suspension of the drug can cause loss of control of the viral load and increase the risk of perinatal transmission and may not result in a reduction of the drug's teratogenicity [10, 11].

The choice of protease inhibitors must be always done in combination with ritonavir, a drug that increases the serum levels

of the PIs for a prolonged and stable period of time, diminishing the risk of viral resistance against the class. Lopinavir (LPV) is the most recommended drug [11] based on its more extensive usage, high viral suppression potential and security profile during pregnancy.

According to the North American guidelines, the use of atazanavir (ATV) must be avoided due to the risk of maternal hyperbilirubinemia. The use of darunavir (DRV) is recommended, the second-most tolerated drug behind LPV [10]. However, the Brazilian guidelines consider the use of ATZ/R as an alternative to the use of LPV/RTV.

The objective of treatment with ARVs is to keep the maternal viral load undetectable and this is because the viral load is directly associated with the vertical transmission of HIV. In a meta-analysis of seven prospective studies of 1,202 pregnant women showing a viral load, near birth, lower than 1,000 copies/ml of HIV RNA in plasma, the vertical transmission rate of the mothers that had done the antiretroviral therapy was 1%, compared to 9.8% in pregnant women who did not use antiretroviral therapy [12].

Pregnant women who have a low risk of progression to AIDS need only prophylaxis to prevent HIV vertical transmission, meaning that they present as asymptomatic with small immunological alterations (LT-CD4+ >500cels/mm³). The recommendation here is to start prophylactic therapy after the first trimester of pregnancy (between the 14th and 28th week), maintaining the use of ARV therapy after the birth. In cases of late diagnosis, it is recommended to start antiretroviral therapy immediately, and in such cases AZT intravenous infusion should also be done.

Cases that evolve with clinical or grave immunological repercussion of the HIV infection possess criteria for the immediate start of treatment, with the objective of treating the disease and reducing the risks of progression [11]. Cases that need retroviral intervention use the same criteria established for adult patients: symptomatic independently of the CD4 count and asymptomatic with a count of CD4 < 500 cels/mm³. Treatment should also be considered for patients with CD4 count above 500 cels/mm³ and with hepatitis B or hepatitis C co-infections, established heart disease (or a Framingham score above 20%) HIV's nephropathy, cancer or viral load above 100,000 copies [11].

Particularities of each group

Nucleoside Reverse Transcriptase Inhibitors During Pregnancy

The nucleoside reverse transcriptase inhibitors induce mitochondrial dysfunction due to their affinity for mitochondrial DNA, interfering with mitochondrial replication and causing depletions and dysfunction. The mitochondria are related to the development of HELLP syndrome and hepatic steatosis in pregnancy. There are reported cases associated with the use of didanosine and stavudine, treatment choices not recommended even for non-pregnant patients [10, 11].

Abacavir can be used when combined with lamivudine, as a daily single dose. Screening for HLA-B5701 and the disclosure of the possibility of collateral motor hypersensitivity effects

is recommended. The use of tenofovir has not showed, when compared to the general population, an increase in congenital defects [11].

Non-Nucleoside Reverse Transcriptase Inhibitors During Pregnancy

Efavirenz is a NNRTI often used in adult patients. However its use is not recommended in the first 42 days of pregnancy because studies have shown a possible drug teratogenicity [10]. A meta-analysis study done by the Pediatric AIDS Clinical Trials Group reported an increase in congenital birth defects in children that were exposed to efavirenz in the first trimester when compared to children that did not have any exposure in the same time period [13-15].

Since efavirenz is a drug commonly used in adult patients and since pregnancy, in most cases, is not detected until after 5-6 weeks, it is recommended not to suspend the use of the drug in patients previously treated so as to avoid loss of control of the viral load, with a recommended ultrasound exam with 18-20 weeks to evaluate fetal progression [14]. In patients that have not yet started antiretroviral therapy, the use of efavirenz before the 6th week of pregnancy can increase the risk of neural tube malformations [14]. However, studies have demonstrated that the incidence of neural tube defects in patients using EFV during the first trimester of pregnancy are similar to the risk found among the general population, therefore EFV is considered a first-choice drug and should be included in the initial antiretroviral therapy during pregnancy [11].

Ripivirine is an alternative to efavirenz in cases of resistance to it. An analysis study about the concentration of the drug in relation to its crossing of the placenta in nine pregnant women and their babies showed a concentration of 53.8 ng/mL of the drug in the umbilical cord's blood, with a serum concentration of 103.3 ng/mL, resulting in an umbilical cord concentration/maternal serum concentration ratio of 0.55 [16]. Therefore this drug seems to be safe to use during pregnancy.

Nevirapine is not recommended due to the adverse effects of the lead-in dosage complex and due to its lower barrier and higher risk of increase in viral resistance. Studies showed that hepatotoxicity and rash, the main side effects that indicate one should not use the medicine, occur approximately 9.8 times more often in adult patients with a count of less than 250 cells/mm³ [17]. In pregnant women, it was observed that the risk for these adverse effects does not increase when compared to the general population, according to a cohort study done with 3,582 pregnant patients resulting in 6.2 of medication suspension due to side effects (3.6% presented with hepatotoxicity and 3.3% with rash) [18, 19]. Since pregnancy can simulate the initial symptoms of a hepatotoxic syndrome - like nausea and vomit - it is recommended to use alternative treatments and, if necessary, the use of this medication must be done in conjunction with transaminases checkups through monthly serum exams until the 18th week, and if there is an increase of transaminases, it is recommended that the use of the drug be suspended [20].

Protease Inhibitors During Pregnancy

In a cohort study done in the United States, 2.2% out of 922

births resulted in malformations after the use of atazanavir [21]. Regarding darunavir, the analysis of 258 births had a percentage of 2.3% births with malformation. The total percentage of live births with malformation in the country is 2.7%, therefore both drugs have a sufficiently low teratogenicity to be considered safe therapeutic alternatives during pregnancy [22].

Saquinavir's use is prohibited due to the necessity of regular ECG follow ups and the possibility of QT wave elongation and indinavir can cause nephrolithiasis and increase the indirect bilirubin levels contributing to the development of hyperbilirubinemia in neonates [11].

Entry and Fusion Inhibitors During Pregnancy

Enfuvirtide and maraviroc can be considered in patients in whom other alternative pregnancy approved ARV therapies have failed. However, security studies and pharmacokinetic studies are necessary to corroborate its recommendation.

The major obstacle for the use of enfurvitida during pregnancy is the risk of resistance that the drug can cause. Seeing that, in patients that have used multiple drugs there is a chance of resistance to the other associated drugs and when used as monotherapy the chances of inducing resistance do enfurvitide increase. Furthermore, due to the fact that the medication has bad posology and necessitates dilution, the adherence to treatment can be faulty.

In a retrospective study of 7 cases utilizing enfuvitide in a 30-day period, the drug has shown to be safe and have good tolerance, seeing that all the newborns presented with negative serology without abnormalities and negative concentration in the umbilical cord. This finding corroborates the description of the other 23 cases in scientific literature where the use of the drug proved to be efficient and safe, especially in patients with viral resistance or with late diagnosis during pregnancy, not presenting with placental transference [23].

Integrase Inhibitors During Pregnancy

Antiretroviral therapies that include raltegravir recommendations are increasing due to its safety during pregnancy and fast drop of the viral load in patients at the end of the pregnancy, reducing the risk of vertical transmission. Other studies demonstrated that there was an increase in transaminases when using the drug, recommending check-ups of transaminases levels and the suspension of the drug if necessary [24, 25].

Raltegravir, according to the PANGA study evaluation, presented good tolerance and efficacy in pregnancy until at least 36 weeks, not presenting with any adverse effects in the newborns due to the mother's consumptions of the drug [26].

Evaluation Of Antiretroviral Induced Fetal Anemia

One of the drugs commonly used in antiretroviral therapy is zidovudine (AZT). The concentration necessary of this drug for the treatment of HIV is toxic for the myeloid and erythroide progenitor cells, justifying the appearance of maternal and fetal macrocytic anemia (seeing as the AZT crosses the placenta barrier

by passive diffusion) during therapy [27]. Concentrations of up to 2% of the drug in the maternal circulation are sufficient to cause damage to the fetus.

Among the general population the evaluation of fetal anemia can be done using invasive and non-invasive propaedeutic methods. Among the invasive ones are amniocentesis and cordocentesis, which require in HIV-positive patients questioning and should be evaluated rigorously due to the main complications, like maternal-fetal hemorrhage, that can worsen the gravity of the disease and increase the risk of vertical transmission [28]. Between the 80's and 90's new non-invasive methods of fetal anemia quantification appeared, for example, the evaluation of peak systolic velocity in the fetal medial cerebral artery (PVS-MCA), using doppler velocimetry [29].

Studies about the arterial compartment doppler velocimetry for research of fetal anemia concluded that anemic fetuses possess an increase in flow velocity due to hemolysis, characterizing hyperdynamic flow due to the decrease in blood viscosity and hematocrit, resulting in an increase of cardiac output to maintain appropriate oxygenation of the fetal organs and tissues. The increase in cardiac output and the vasodilation are the main mechanisms through which the fetus tries to maintain oxygen delivery to the various organs. However, fetuses in more advance stages of anemia can exhibit alterations in cardiac function and are therefore incapable of increasing their cardiac output [30, 31].

Delivery Methods in HIV Positive Pregnant Women

Various studies demonstrated the benefits of elective Cesarean-section (done before the beginning of labor when the chorioamniotic membranes intact) as it has shown a decrease in HIV vertical transmission (VT), when compared with other delivery methods. The Cochrane group did a systematic review, published in 2005, to evaluate the effectiveness and safety of elective C-section in the prevention of VT in women who did not use ARV therapy during pregnancy and those who only used AZT. The risk factors associated with transmission were detectable viral load, short duration of ARV use and pre-term labor [32].

After the evaluation of the woman by the obstetrician and by the infectologist, it is recommended to inform the woman about the risks and benefits of the chosen delivery method. During clinical evaluation, immunological state (LT CD4 count) and virological state (quantification of viral load) monitoring exams should be included for HIV-positive pregnant woman, and should be mandatory in the beginning of pre-natal care and in the 34th week so as to better define the delivery method. The criteria for choice of the delivery method (vaginal or cesarean) include a viral load and the gestational week number. The evaluation by the obstetrician is done during the 34th gestational week and takes into account the patient's viral load. If it is $\geq 1,000$ copies/ml or unknown the recommendation is to perform elective C-section.

In these women, even if labor has started, the C-section should be the selected delivery method provided that cervical dilation is 3-4 cm or less and the amniotic membranes are intact. If the viral load is $\leq 1,000$ copies/ml or undetectable there is a possibility for vaginal delivery, since birth by C-section only applies when there

is obstetric indication [33].

If there is an indication for C-section, some precautions must be taken, such as the correct establishment of gestational age, adequate revision of injectable zidovudine administration time (at least 3 hours before the beginning of C-section) and ligature of umbilical cord immediately after the baby's delivery. If the chosen method is vaginal delivery, the focus should be in the immediate ligature of umbilical cord after the babies delivery, avoidance of invasive and surgical procedures, like episiotomy, amniocentesis, forceps use, vacuum extractor and precipitate amniotomy, and preventing the patient from staying for more than four hours with rupture membranes or having prolonged labor (more than 12 hours) [34].

In HIV transmission prophylaxis during labor, the indicated drug is injectable zidovudine, that should be administered from the beginning of labor until the clamping of the umbilical cord, in all pregnant women, except those with a viral load undetectable after 34 weeks.

Due to the risk of anemia in newborns using zidovudine, it is recommended that a newborn complete a blood panel, to monitor the baby until the 16th week after birth. Oral consumption of AZT should be only used in situations where the injectable AZT is not available at the time of delivery [34].

Prematurity Risk

The ARV therapy used in pregnant women can include the use of IP, which is associated with low birth weight and prematurity. The maternal characteristics that are most associated with pre-term labor and prematurity (birth before 37 complete weeks of pregnancy) and low birth weight (birth weight of less than 2.500g) are clinical stage of maternal HIV disease, maternal viral load at the beginning of study, diabetes, delivery method and hypertension [35].

Kourtis et al., published an analysis in which they selected studies that had two comparative groups: HIV-positive pregnant women using therapy and HIV-positive pregnant women not using therapy. Five cohort studies were included, comparing the use of ARV and the increase in pre-term labor prevalence. The only significant association was the increased risk of prematurity when ARV therapy with IPs was used, in comparison with therapies without IPs [36].

A study showed that 18.6% of HIV positive mothers who used IPs in their first trimester had pre-term labors, showing an increase in risk of prematurity with the use of IPs during the first trimester in comparison to ARV therapy without IPs and that instead uses NNRTIs or monotherapy. The IPs most associated with prematurity are saquinavir and ritonavir.

Other studies showed a prematurity rate of up to 20% when the pregnant women uses protease inhibitors [37].

Prematurity and low birth weight are factors associated with an increase in perinatal morbidity and mortality, related to a higher risk of HIV vertical transmission [36]. Premature babies can be more susceptible to infections by HIV because they possess

a more permeable skin and an immature immune system, besides an increased production of inflammatory mediators. The indicators of neonatal mortality are intimately associated to gestational age, and the more premature, the higher the mortality rate. It was concluded that prematurity is related with ARV use during pregnancy, especially IPs. However, the use of ARVs is extremely important for the decrease in HIV maternal-fetal transmission rates.

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