

# HIV medication to prevent fetal infection during pregnancy

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## ABSTRACT

When it has been declared a global epidemic, HIV infection became a challenge for medical world. Even if there is only one healed case cited in literature, treatment for HIV-infection have evolved during time leading to very good results in disease control and limitation of virus transmission. When it comes for viral transmission, an essential research topic became the prevention of mother to fetal transmission. In the long run, many discovered antiretroviral drugs proved to be efficient in controlling HIV infection during pregnancy and thereby in reducing the risk of viral transmission to the fetus. But along with use of the HIV-treatment in pregnancy, many questions have appeared. Are the drugs safe for the fetus, or are there any adverse pregnancy outcomes? Should the treatment be adjusted for the desired results in pregnancy, or should the initial treatment be changed when the pregnancy is diagnosed? Many retrospective or prospective observational studies and comparative studies have been conducted in order to answer those questions and to analyze the efficacy and the safety of mostly used antiretroviral drugs in pregnancy. This article reviews the existing studies, guidelines and recommendations regarding the combined antiretroviral HIV treatment during pregnancy for fetal infection prevention.

**Keywords:** HIV, antiretroviral therapy, NRTI backbone, preterm delivery, pharmacokinetics

## INTRODUCTION

In 1983, it was first proven that the etiology of acquired immunodeficiency syndrome (AIDS) was a virus subsequently named human immunodeficiency virus (HIV) [1]. Even if, the disease was first diagnosed among homosexual pairs in the United States, it has then become a global epidemic. The prevalence is different between developed countries and low-income countries, East and Southern Africa being the most affected region in the world, with 20,6 million people living with HIV in 2020, 100 times more cases than in developed countries [2]. For this reason, the prevalence in the antenatal population varies from 0,01-0,2% in the first category to 29% in the other one [3]. When HIV infection is present in pregnancy, special management is required antenatally, intrapartum and postpartum because an un-

treated disease could have serious impact on both mother and child. One of the most important aspects of HIV infection management during pregnancy is the prevention of mother-to-child transmission (MTCT). This involves three essential strategies to be applied: 1. The use of antiretroviral therapy antenatal, intrapartum, and neonatal; 2. Avoiding breastfeeding; 3. Reduction of the obstetric interventions intrapartum and taking into account the caesarean section (CS) [4,5]. This review article will focus on antiretroviral therapy during pregnancy.

## MATERIALS AND METHODS

PubMed database was searched for studies published during the last 10 years, written in English, that analyzed HIV medication during pregnancy.

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For the search in the PubMed database, combination of the following keywords was used: ‘HIV’, ‘pregnancy’, ‘mother-to-child-transmission’, ‘antiretroviral therapy’, or ‘SIDA’.

## HOW COULD HIV INFECTION AFFECT PREGNANCY?

Over time, some negative effects were observed in pregnant women HIV-infected. These include increased spontaneous miscarriages, increased perinatal mortality, intrauterine growth restriction, low birth weight, chorioamnionitis [6] and also increased frequency and exacerbation of many infections in pregnancy including herpes simplex, human papillomavirus, candidiasis, bacterial vaginosis, cytomegalovirus, toxoplasmosis, hepatitis B and C, urinary tract infections and pneumonia. On the other hand, HIV infection course might not be significantly affected by pregnancy. During pregnancy, it could be observed a reduction of CD4 cell count which is due to hemodilution, but stable levels of HIV RNA are seen most of the time [7].

## MEDICATION USED IN HIV TREATMENT

Antiretroviral medication can be classified into 6 major categories depending on the action mechanism: Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease inhibitors (PIs), Integrase Strand transfer inhibitors (INSTIs), Fusion inhibitors and Coreceptor antagonists. Antiretroviral regimens usually contain 2 nucleoside reverse-transcriptase inhibitors and a third agent from another class [8].

## TREATMENT OF HIV INFECTION IN PREGNANCY

The efficacy of antiretroviral treatment in reducing the risk of mother to child HIV transmission was proved in numerous studies to date. Also, during pregnancy, the standard treatment for HIV-infected women, no matter the CD4 count or the viral load, includes a combination of at least three antiretroviral drugs [9]. According to The US Department of Health and Human Services, the initial recommendation is the use of two nucleoside reverse transcriptase inhibitor (NRTI) in combination with a protease inhibitor (PI) or an integrase inhibitor [9].

## WHEN TO INITIATE ART?

Most of the time, when pregnant women are known having HIV infection, they will have an antiretroviral therapy (ART) assigned. In this situation, what should be further done is to evaluate if the viral load is controlled under the existing therapeutic schema or if some adjustments are needed.

But when HIV diagnosis is first established during pregnancy, the ART should be initiated as soon as possible. It has been proven that earlier initiation of ART in treatment-naïve pregnant women increases the chances of viral suppression by the time of delivery, thereby decreasing the risk of fetal transmission [10].

## SELECTING ART REGIMEN

Choosing the ART regimen might be challenging during pregnancy. It should not only treat the maternal HIV infection but moreover it should prevent perinatal transmission, while considering all physiological changes that appear during pregnancy and modify antiretroviral exposure and minimizing toxicity for mother and fetus.

The pharmacokinetic data of antiretroviral drugs are very important for appropriate dosing during pregnancy. If lower drug concentrations are obtained, HIV RNA rebound and virus resistance could appear and therefore an increased risk of infant viral transmission. On the other hand, increased exposure might lead to fetal toxicity or maternal adverse effects. Apart from Efavirenz, an NNRTI, which was reported to cause birth defects when used in the first trimester and is now recommended to be avoided, most antiretrovirals are part of medication used during pregnancy.

When initiating ART, there should be taking into consideration that few toxic manifestations can appear such as anemia, hyperlipidemia, fat redistribution, insulin resistance, or mitochondrial toxicity related effects including lactic acidosis, pancreatitis, peripheral neuropathy, myopathy and cardiomyopathy. This is the reason why hematological and biochemistry parameters should be carefully monitored during treatment [11].

Another important factor to be considered is the transplacental passage of each drug. NRTIs have an easy passage across the placenta, that is why guidelines recommend combinations including Lamivudine, Emtricitabine, Tenofovir or Abacavir. Among NNRTIs, Nevirapine seems to have the greatest placental transfer, while among INSTIs, Raltegravir has a high transfer rate. In contrast, protease inhibitors have a poor transplacental transfer [12].

## HOW TO MONITOR INFECTION EVOLUTION UNDER TREATMENT DURING PREGNANCY

When ART is established during pregnancy, a first viral load should be measured before the treatment beginning, then 2-4 weeks after initiation. After that, at least one viral load measurement every trimester is recommended and towards pregnancy end, it should be determined at 36 weeks and at delivery [13].

## PREGNANT WOMEN ALREADY ON ART

When ART has been already initiated before pregnancy and the viral suppression is achieved, the regimen should be continued, no matter if it is not one of the preferred regimens in pregnancy. However, when protease inhibitors are included, dose adjustment might be necessary.

When viral suppression is not achieved under ART initiated before pregnancy, the reason for this failure should be found out. In this situation it is essential to test if drug resistance has occurred or if the patient is not adherent to the treatment. If resistance is discovered, the regimen should be changed, but if the problem is the adherence, the physician should take into consideration a regimen with a once daily administration.

## ART CHOICE FOR TREATMENT-NAIVE PATIENTS

### 1. NRTI backbone

There are few preferred combinations of NRTI backbone in pregnancy and those include: Tenofovir Alafenamide-Emtricitabine (TAF-FTC), Tenofovir Alafenamide - Lamivudine (TAF-3TC), Tenofovir Disoproxil Fumarate - Emtricitabine (TDF-FTC), Tenofovir Disoproxil Fumarate – Lamivudine (TDF-3TC) and Abacavir – Lamivudine (ABC-3TC) [14]. Because studies have shown that pharmacokinetics of these drugs do not change significantly during pregnancy, according to general recommendations, there is no need for dosage adjustments [15].

One pooled analysis performed in Europe between 2008-2014 on over 5700 pregnancies in HIV-infected women that started ART during pregnancy, showed that there is no increased risk of preterm delivery, when NRTI backbone TDF containing was used. Moreover, the study showed that a SGA (small for gestational age) fetus is less likely to appear when combinations such as ABC-3TC or TDF-XTC are used in comparison with ZDV-3TC combination. Therefore, TDF-XTC combination is considered safe and is the first-line recommendation in pregnancy in WHO guidelines [16].

### 2. The third drug in the combination

In the treatment-naïve pregnant women, the choice of the third drug is preferable to be an integrase inhibitor or a boosted protease inhibitor. Between integrase inhibitors, Dolutegravir and Raltegravir are recommended in pregnancy. Protease inhibitors that could be a choice in pregnancy are Ritonavir-boosted atazanavir and Ritonavir-boosted darunavir. As a third agent, a choice could also be a NNRTI such as Efavirenz or Rilpivirine

#### 2.1. Integrase inhibitors containing regimens

The IMPAACT 2010/VESTED, a multicentric, randomized phase 3 trial, compared the efficacy and adverse events between three combinations of ART

drugs during pregnancy, 2 of them containing Dolutegravir (dolutegravir-emtricitabine-tenofovir alafenamide; dolutegravir-emtricitabine-tenofovir disoproxil fumarate and efavirenz-emtricitabine-tenofovir disoproxil fumarate). The trial revealed that Dolutegravir-containing regimens lead to significantly higher rate of viral suppression at delivery, a significantly shorter period to viral suppression and fewer infant deaths than the efavirenz-emtricitabine-tenofovir disoproxil fumarate combination. According to this study, dolutegravir-emtricitabine-tenofovir alafenamide had a better safety profile, with lower frequency of preterm deliveries than the other two, without the reasons to be known. An observation that could bring an explanation could be that when this regimen was used, the patients had the greatest weight gain, closer to the recommended weight gain in pregnancy and not insufficient as observed in the other two regimens (being known that inadequate weight gain in pregnancy is related to preterm birth and small for gestational age infants) [17]. None of the regimens lead to a greater occurrence of maternal or infant events grade 3 or higher [18]. Some advantages of Dolutegravir-containing regimens include not only the rapid viral decline as previously observed, but also that it is administered as one daily dose and has a good tolerability. Nowadays, Dolutegravir is a preferred agent to be used in pregnancy [19].

Regarding Raltegravir choice as the third drug in cART, a study conducted in Rio de Janeiro demonstrated that significantly more participants on Raltegravir reached an undetectable viral load near delivery compared to the other 2 regimens, that is 87% versus 73% in efavirenz-containing regimen and 70% in protease inhibitor containing regimen [20].

Recently, another integrase inhibitor called Elvitegravir was studied for its efficacy and safety in pregnancy. In 2017, the recommendations were against this drug use in pregnancy, because data were limited [21]. Recently a multicentric analysis revealed that this drug was well tolerated, lead to high viral suppression rates (81,3%) and a low rate of perinatal HIV transmission. Even if further investigations are needed, taking into account that Elvitegravir is efficient, easily administered and well tolerated, this drug might be a good option as the third drug in ART combinations in the future [22].

Integrase inhibitor containing regimens are also the first choice of treatment when the women present late in pregnancy, after 28 weeks of gestation, with high viral load that increases the risk of viral transmission if the treatment is not capable of rapid viral suppression [23].

#### 2.2. Protease inhibitors containing regimens

When taking into consideration the choice of a protease inhibitor (PI), it should be kept in mind

that they can contribute to the uteroplacental pathology, in particular Rotinavir-boosted lopinavir. According to one review published by Dunk et al, some protease inhibitors dysregulate maternal endocrinology and compromise placenta. Therefore, US and European guidelines recommend Ritonavir-boosted lopinavir to be avoided in pregnancy [24]. Moreover, another meta-analysis revealed that PI exposure during pregnancy could increase the risk of preterm birth, coming with the recommendation of replacing PI during pregnancy with other ART drugs [25]. Additionally, some experts consider that exposure to protease inhibitor is a risk factor for glucose intolerance and when drugs from this class are used during pregnancy, screening for gestational diabetes should be done earlier in pregnancy [14].

Despite these observations, there are two PI used in pregnancy: Ritonavir-boosted atazanavir which is administered once daily and Ritonavir-boosted darunavir which require twice daily dosing.

### 2.3. NNRTIs containing regimens

An alternative for use with a dual-NRTI backbone is Efavirenz, a once-daily NNRTI. Even if, there have been some concerns regarding the possibility to cause neural tube defects, in the long run, reassuring data have accumulated, so that its usage is not restricted during pregnancy [26]. Another NNRTI alternative is Rilpivirine. The advantage is that it is found as a single-pill combination with tenofovir and emtricitabine. Its use is however limited to individuals with baseline HIV viral load < 100 000 copies/ml and CD4 cell count > 200 cells/microL [14].

An observational study including 794 HIV-infected pregnant women in Italy, analyzed if there are significant differences between ISTI, PI and NNRTI used as third agent, regarding effectiveness and safety. No major differences were found between those three classes. As particularities for each of

these classes, it was observed that when using PI, pregnant women were less likely to be virologically suppressed in the third trimester and that their levels of bilirubin and triglyceride were higher. Moreover, ISTI use was associated with a lower rate of low birthweight [27].

## CONCLUSIONS

When HIV infection is present during pregnancy, the appropriate treatment should be established or adequately adjusted as soon as possible. Studies have proven that combined antiretroviral therapy can be used during pregnancy and by significantly reducing the viral load can decrease the risk of mother to fetal viral transmission to almost zero. Similar to the treatment in non-pregnant patient, the recommended regimen should contain a combination of 2 NRTI backbone and a third drug, preferably an integrase inhibitor, or a protease inhibitor. During pregnancy should be always keep in mind that doses should be adjusted because drugs pharmacokinetics will be modified along with physiological changes in pregnancy. The first line recommendation for NRTI backbone in pregnancy is Tenofovir with either Emtricitabine or Lamivudine. For the third drug choice, an integrase inhibitor is preferred most of the time, Dolutegravir and Raltegravir being the first option. Drug toxicity should also be monitored during pregnancy, for both mother and child safety. The most frequently debated possible pregnancy adverse effects of ART are preterm delivery and insufficient fetal growth, but more studies should be done for certain conclusions. However, what all studies showed us is that HIV infection transmission from mother to fetus can be prevent by correct treatment during pregnancy.

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