The Safety and Effectiveness of Protease Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors for Pregnant Women

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Abstract. Background. This article investigated the efficacy and safety of antiretroviral medication (ART), namely protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI), used by HIV/AIDS pregnant women. It emphasizes the relevance of ART management throughout pregnancy for maternal and child health, aiming to teach doctors and improve outcomes at the maternal and child levels. **Objective.** To study how HIV-infected pregnant women's PI and NNRTI efficacy and clarity affect mother's and baby's health. **Method.** A systematic review was undertaken between 2002 and 2021 to assess the similarity groups of HIV-positive pregnant women and their fetuses. The analysis compared the effects of PI-containing and NNRTI-based ART. Over 45,000 pregnant women from 27 nations were analyzed in studies, with each receiving a distinct technique rating. **Results.** The systematic review included 10 studies in total, with 45,427 women participating. The findings revealed that there was no significant connection between PIs and NNRTIs for various fetal/neonatal outcomes. Therapeutic drug monitoring should be performed on PIs and NNRTI regimens with a small therapeutic window, respectively. The study of antiretroviral medicines with pregnant women indicated that both drug classes were safe throughout pregnancy, with PI-based regimens showing greater efficiency in achieving viral suppression. Hearing early ART initiation resulted in better neonatal outcomes. **Conclusion.** ART therapy for HIV-positive pregnant women must prevent toxicity and inadequate medication distribution. PIs reduce perinatal risk and inhibit viruses. Understanding patient-drug interactions is crucial because starting ARTs late is dangerous. Go-ahead tracking enhances mother and infant health, HIV-related pregnancy outcomes, and HIV management.

Keywords: Protease inhibitors; non-nucleoside reverse transcriptase inhibitors; Pregnancy; Antiretroviral therapy.

1. Introduction

Human immunodeficiency virus (HIV) remains a major disease worldwide. Antiretroviral therapy (ART) has been demonstrated to be a viable technique for improving the prognosis of patients in various HIV populations, including pregnant women who have received education and now have the opportunity to get this treatment [1]. On the other hand, the security and confidence of this ART application during pregnancy are ranked alongside safety and dependability. This study will conduct a review of the literature on the effectiveness and severity of PIs and NNRTIs used by HIV mothers.

Human immunodeficiency virus (HIV) continues to pose a global health burden, and one of the most advanced discoveries in the healthcare system is the present treatment of HIV-positive pregnant women, known as antiretroviral therapy (ART). Effective HIV management during the prenatal period is critical to both the mother's health and the prevention of transmission from mother to child (MTCT) [2]. The physical changes that the body undergoes during pregnancy will certainly alter the pharmacokinetics of antiretrovirals used to treat HIV, resulting in increased blood levels and prolonged drug retention in the body [3]. The changes cause drug concentrations to become high and possibly fall outside the acceptable range of drug safety and efficacy. TDM has been recognized as an important method of adjusting doses to ensure that antiretroviral levels do not exceed their therapeutic windows, particularly in the case of PI and NNRTI medicines, which frequently have limited therapeutic windows [4]. Several reports, including pregnancy studies, show that PIs and NNRTIs are both safe for both mothers and their offspring [5]. A review of reported cases revealed

that PIs and NNRTIs were found to be effective by a study that showed a reduction in preterm birth and weight at birth compared to other treatments. However, in another study by Roustit et al. (2008) [6], there was no relationship seen in cases of congenital disabilities in newborns exposed to PIs or NNRTIs, fetching caution in the case of mood-altering problems that may occur from individual efavirenz.

From the efficacy viewpoint, the study established that PI antiretroviral regimens could be the best as opposed to NNRTIs, including the poor response to antiretroviral therapy and MTCT prevention [7]. NNRTI resistance manifested could be reduced, and the chances of its emergence decreased as a consequence of the higher genetic barrier to resistance of PIs. This factor has been proposed as a fundamental explanation of the enhanced anti-HIV activity of PIs, particularly in settings manifesting high levels of pre-existing NNRTI resistance [8]. Research showed that earlier medical assistance of ART, ideally before pregnancy or during the first trimester, is connected with the rate of MTCT at a reduced level with better perinatal outcomes, while later initiation of ART is connected with the rate of MTCT at a higher level with worse perinatal outcomes [9]. Late ART start makes it more likely to have premature delivery, low birth weight, and difficulty in adequately managing viral load [10]. Customized treatment should be made by taking into account the specific biological markers of the patient, the resistance factors that the pathogen has developed to unique drugs, expected side effects, and drug interactions.

2. Methodology

The research was conducted using a systematic examination of PubMed, Reprotox, the Clinical Trial Registry (clinicaltrials.gov), and abstracts from HIV conferences held between January 1, 2002, and October 29, 2021. The study examined perinatal outcomes such as spontaneous abortion, stillbirth, congenital abnormalities, PTB (<37 weeks of gestation), VPTB (<32 weeks of gestation), LBW (<2500 grs), VLBW (<1500 g), SGA, and VSGA. The connection between prenatal exposures to PI-based ART versus NNRTI-based ART was assessed for each adverse perinatal outcome. The researcher selected 49,171 articles for a full reading. The selected studies involved 45,427 pregnant women from 27 different nations. Nineteen studies were undertaken in high-income countries and thirteen in low-income countries. Only one randomized controlled study was chosen, with the remainder being cohort studies. Overall, ten studies received a high rating for methodological quality. The study sample included 75 to7, 009 pregnant women aged 26 to 33, with a median CD4+ count of 154-638 cells/mm3.

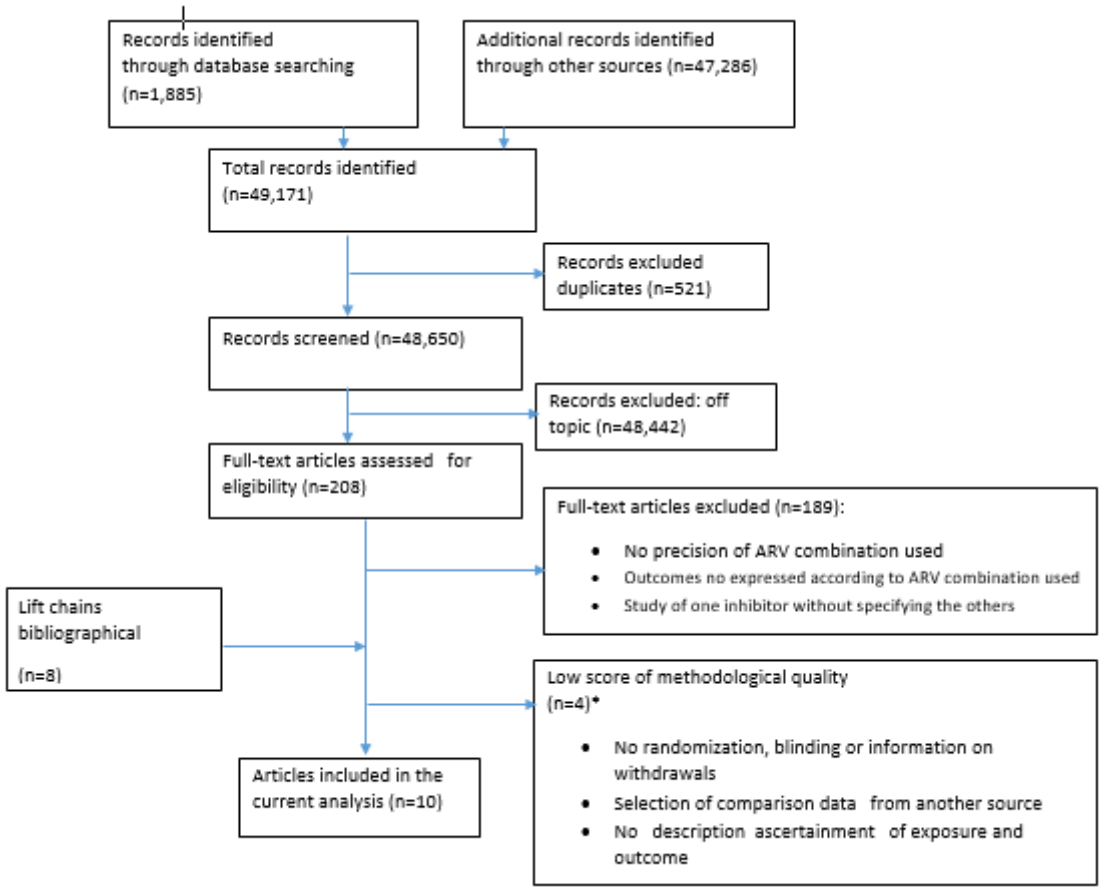


Figure 1: Flow-chart of study selection process according to PRISMA guidelines
*Four articles had low methodological quality's score

3. Results

This reivew included 10 studies, which met our criteria (Figure 1). There was no significant difference between PI and NNRTI prenatal exposure for VPTB, LBW, SGA, stillbirth, and congenital anomalies. However, it was equivocal for PTB, and PI-based ART is associated with a considerably higher incidence of VSGA than NNRTIs. Therapeutic drug monitoring (TDM) is critical, especially for protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), which have a limited therapeutic window, to ensure optimal drug exposure while avoiding unwanted effects or therapy failure. PIs and NNRTIs are safe to use during pregnancy, with no substantial increase in the incidence of congenital impairments in exposed infants. PI-based regimens were more effective than NNRTI-based regimens in suppressing viral load, which could be attributed to PIs' stronger genetic resistance. Early beginning of antiretroviral medication (ART), ideally before pregnancy or during the first trimester, was linked to decreased incidence of MTCT and better perinatal outcomes, including a lower risk of preterm birth and low birth weight. The table below summarizes the findings.

Table 1: Characteristics of included trials

Study	Setting	Sample Size	Measuring Outcomes	Key Findings
Saint-Lary et al. (2021) [1]	Pharmacovigilance database analysis	45,427 pregnant women from 27 countries	Spontaneous abortion, stillbirth, congenital abnormalities, preterm birth, low birth weight, small for gestational age	No significant association between PI vs. NNRTI exposure for most outcomes, but increased risk of very small for gestational age with PI-based ART.
Saint-Lary et al. (2023) [2]	Systematic review and meta-analysis	45,427 pregnant women	Adverse perinatal outcomes	PI-based ART associated with increased risk of very small for gestational age compared to NNRTI-based ART. No significant differences for other outcomes.
Mirochnick & Capparelli (2004) [3]	Review	-	Pharmacokinetics of antiretrovirals in pregnancy	Physiological changes in pregnancy alter pharmacokinetics of antiretrovirals, highlighting the importance of therapeutic drug monitoring.
Portwood et al. (2022) [4]	Systematic review and meta-analysis	-	Perinatal outcomes with combination ART vs. monotherapy	Differences in perinatal outcomes between combination antiretroviral therapy (ART) and monotherapy
Beck et al. (2024) [5]	Systematic review and meta-analysis	-	Adverse perinatal outcomes associated with ART classes	Perinatal outcomes associated with different classes of ART in pregnant women living with HIV
Roustit et al. (2008) [6]	Review	-	Pharmacokinetics and TDM of antiretrovirals in pregnancy	Pharmacokinetics and therapeutic drug monitoring of antiretrovirals during pregnancy
Floridia et al. (2020) [9]	Observational study	-	Pregnancy and neonatal outcomes with different ART classes	Pregnancy and neonatal outcomes in HIV-positive women exposed to different ART classes-

Bello et al. (2022) [10]	Observational study	-	NNRTI resistance levels in pregnant women with recent HIV infection	PI-based regimens were found to be more effective than NNRTI-based regimens in achieving viral load suppression
Sexton et al. (2022) [11]	Systematic review and meta-analysis	-	Adverse perinatal outcomes associated with timing of ART initiation	ART associated with lower rates of mother-to-child transmission-
Sturt et al. (2010) [12]	Systematic review	-	ART for treating HIV in ART-eligible pregnant women	ART associated with lower rates of mother-to-child transmission

Note:
PIs: (Protease Inhibitors)
NNRTIs: (Non-Nucleoside Reverse Transcriptase Inhibitors)
HIV: (Human Immunodeficiency Virus)
ART: (Antiretroviral Therapy)
MTCT: (Mother-to-Child Transmission)
TDM: (Therapeutic Drug Monitoring)
PTB: (Preterm Birth)
VPTB: (Very Preterm Birth)
LBW (Low Birth Weight)
VLBW: (Very Low Birth Weight)
SGA: (Small for Gestational Age)
VSGA: (Very Small for Gestational Age)
PRISMA: (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)

4. Discussion

4.1. Pharmacokinetics of Antiretrovirals in Pregnancy

The occurrence of HIV infection during pregnancy exerts a substantial influence on the pharmacokinetics of antiretroviral medications employed in treatment, hence potentially affecting the safety and effectiveness of those medications. Physiological changes occurring in pregnancy are numerous and result in varied absorption, distribution, metabolism, and excretion of drugs among pregnant women. A significant physiological transformation that occurs during pregnancy is the elevation of the blood volume, which results in the decrease of drugs that are bound to the plasma proteins. This occurrence could result in significantly larger quantities of the drug in its unbound and active forms, leading to increased side effects or toxicity. Besides, pregnancy influences the activity of drug-metabolizing enzymes and transporters, which turns out to be a reason for changes in the processing and clearance of some antiretroviral drugs.

Renal function changes throughout pregnancy, as does the rate of glomerular filtration and renal blood flow. It can lead to a sudden increase in the clearance of medications that are typically eliminated through the kidneys, resulting in a significant decline in their potency. Knowing these factual alterations makes it paramount to closely monitor the dose level to avoid adverse effects on the drug or the failure to achieve the optimal drug effect.

The special value of TDM is comparable to PIs/NNRTIs, which comprise a small therapeutic window and also resist physiological changes during pregnancy. For instance, the pharmacokinetics of PIs such as lopinavir and atazanavir have received particular interest during pregnancy because of drug level reduction, posing inadequacy issues if not properly monitored and adjusted. By practicing

TDM and tailoring the dose modification approach, health practitioners provide optimal exposure to drugs that are safe and effective for pregnant women with HIV because such exposure alleviates the risk of adverse side effects or treatment failure. This strategy benefits patients and prevents mother-to-child transmission of HIV during pregnancy, labor, and delivery services that can be delivered in time.

4.2. Safety of Protease Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors

Findings on pregnancy safety for both PIs and NNRTIs as far as this relates to the women's health and that of the unborn children is essential. The maternal safety assessment helps identify and manage pregnancy risks. During pregnancy, an antiretroviral therapy safety issue is relevant because the negative reaction to the substance can influence the mother and her developing child. Besides questions about the effectiveness of the drugs, there are also safeties for the mother and fetal development that should be considered. Previously, the first belief was that PI is unable to traverse the placental barrier. However, this notion has been refuted by scientific research.

4.3. Effectiveness of Protease Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors

The effectiveness of ART regimens during pregnancy is typically assessed by measuring viral load suppression and preventing Maternal-to-Child Transmission (MTCT) of HIV.

4.3.1 Viral Load Suppression

The most important goal in HIV treatment during pregnancy is successful and uneventful viral suppression, which marks the improvement of maternal health in the first place and the prevalence of MTCT in the last place. Studies demonstrated the efficacy of a PI-containing antiretroviral regimen being higher than an NNRTI-containing regimen in the management of HIV by doctors [11]. It could be due to the higher genetic barrier to the resistance of PIs, which permits these drugs to act without the formation of resistance mutations.

Considering the successful treatment of individuals in areas where NNRTI doses are naturally high, PIs are particularly useful when genetic barriers leading to resistance are involved. In these set-ups, NNRTI-containing regimens can be less potent due to pre-existing resistance, whereas PI-based regimens may be a better option for highly effective viral suppression. Providing viral replication suppression during pregnancy is of great importance for the health of the mother, and eliminating MTCT and consequently reducing the chances of being subjected to drug resistance, thus posing a risk of being unreceptive to further treatment options.

4.3.2 Prevention of Mother-to-Child Transmission (MTCT)

MTCT of HIV (Preventing Maternal to Child Transmission) is one of the main objectives in the management of HIV during pregnancy. Two of the HIV-1 drug classes, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been found to be effective when used in combination with other ART treatment medications in avoiding the MTCT of HIV [12]. However, another research study has found that the PI-based system, which entails the NNRTI-based system, has lower rates of MTCT in relation to the PI-based regimen. Hence, the data being still restrictive, highlighting mechanisms underlying this observation could be of great importance to MTCT prevention programs.

One possible explanation for the projected PI regimen superiority in decreased MTCT incidence could be because these regimens provide higher efficiency in decreasing viral loads throughout pregnancy. Thus, for PI-based drugs, the nature of viral reproduction could be altered, and the chance of vertical transmission from mother to child during a time of pregnancy, labor, and delivery and through breastfeeding would be reduced. Tabulating an untraceable level of viremia-viral replication in an individual is an essential element of preventive MTCT because it reduces the probability of viral transmission through mother-to-infant contact.

The extended genetic barrier to resistance of PIs, in particular when co-administered with other antiretroviral medications, can be utilized as an added instrument of resistance prevention, which

impedes mother-to-child transmission. With regards to the settings whereby the NNRTI resistance is quite elevated, the Pi-based regimens provide a strong option for feasibly achieving viral suppression and distorted vertical transmission. Raising the level of resistance to enter the PI again could kick out some pre-existing resistance mutations, which could complicate the work of NNRTI for MTCT prevention. However, the specific mechanisms that are implicated in the commonly believed effectiveness of PI-based regimens in lowering the potential risk of blocking the parasite in newborn babies are yet to be fully understood. So, further studies are needed to provide a more informed conclusion. Although PI-based regimens have some advantages, the choice of antiretroviral medication during pregnancy should be customized based on a variety of considerations, such as maternal health status, drug resistance trends, potential drug interactions, and potential side effects. Furthermore, once infected, an approved regimen is highly efficient in managing and maintaining virus-free HVs while also reducing the risk of MTCT.

4.4. Timing of ART Initiation and Adverse Perinatal Outcomes

Antiretroviral medication (ART) timing during pregnancy is extremely important since it has the potential to alter the level of unpleasant experiences in the neonatal setting. It has been discovered that assisted reproductive technology is mostly introduced during pregnancy, particularly in the third trimester. It is concluded that the initiation of antiretroviral therapy (ART) for HIV infection in women, especially in the early stages of pregnancy, is a crucial factor in initiating ART at an early stage because it reduces the risk of HIV transmission to newborns.

Many factors are considered as the key explanations that stand behind the sediment that has the most fetal outcomes during the gestation period. Firstly, attempting ART later in pregnancy is insufficient for the therapy to eliminate the virus from the mother's body effectively. The treatment must suppress the viral load during this key life process to lower the danger of mother-to-child infection and to prevent the development of health complications for the mother [13]. Timely ART initiation can come up during high viral load, and research suggests that this can be associated with an elevated probability of preterm labor and low birth weight. The pharmacokinetics of drugs during pregnancy, with their physiological alterations, reduce the effectiveness and safety of ART, especially when avoided before they cause any major and more pronounced changes.

ART initiation less than a year before conception or during the first trimester is preferable if possible; this reduces the risks of MTCT and also mitigates the adverse effects of later ART initiation, which are related to long-term unsuccessful suppression of the virus. Healthcare providers must help these women to start the use of ART as soon as possible, monitor their adherence to it during pregnancy, and ensure favorable maternal and fetal outcomes.

5. Conclusion

ART management of HIV-positive pregnant women is a mission that requires the majority of medical personnel to be always vigilant for the safety and efficacy of ART regimens. Protease inhibitors (PIs) are far superior to non-nucleoside reverse transcriptase inhibitors (NNRTIs), which HIV-positive pregnant women commonly use. PIs have also been shown to have a risk-lowering effect on perinatal adverse outcomes; high rates of viral load suppression can effectively prevent the transfer of the virus from mother to child. Indeed, besides individual patient features, drug resistance and drug interactions can also play a critical role in deciding the right combination of drugs in ART therapy. Experts suggest ART to start early before the pregnancy to reduce the risk of negative outcomes. Ongoing investigation and long-term tracking of maternal and infant outcomes remain vital to enhance the established chief health plan in the situation of HIV during pregnancy, aiming at desired outcomes for the women and their newborn babies.

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