DOI: https://doi.org/10.61841/6a01rq38 Publication URL: https://nnpub.org/index.php/MHS/article/view/2104

THE EFFECT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND ANTIRETROVIRAL THERAPY ON THE RISK OF PRE-ECLAMPSIA : A TEN YEARS SYSTEMATIC REVIEW

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ABSTRACT

Background: *Human immunodeficiency virus (HIV) infection affects 25% of the US population, with women being the most likely to receive a diagnosis during their reproductive years. Pregnant HIV-infected women are recommended to start antiretroviral therapy (ART) during pregnancy, regardless of CD4+ cell count. Research suggests that HIV infection may reduce the risk of pre-eclampsia (PE). Despite PE being the cause of 42,000 maternal fatalities annually, pregnant women living with HIV are less likely to develop pregnancy hypertensive problems.*

The aim: *This study aims to determine the effect of HIV and antiretroviral therapy on the risk of PE.*

Methods: *This work demonstrated compliance with all standards by means of a comparison with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Consequently, experts were able to guarantee that the study was as current as feasible. Publications released in the years 2014–2024 were considered for this search strategy. To do this, a variety of internet reference sites were used, including ScienceDirect and PubMed. Review articles, previously published works, and partially completed works were all selected not to be considered.*

Results: *When we searched the PubMed database, we found 33 papers, but when we searched ScienceDirect, we found 92 publications. Title screening produced a total of 14 articles for PubMed and 23 articles for ScienceDirect in the search results. Eight papers from PubMed and ten from ScienceDirect made up the total of the papers we compiled. Four reviews, four duplicates, and one with insufficient results were all excluded. Nine studies that satisfied the requirements were finally included.*

Conclusion: *This systematic review found that maternal HIV infection and not using antiretroviral therapy reduced the risk of PE. However, further investigations with more well-designed studies with larger sample sizes are still needed.*

Keywords: *HIV, antiretroviral therapy, HAART, pre-eclampsia, pregnant woman.*

INTRODUCTION

The human immunodeficiency virus (HIV) most likely became infected in humans during the course of the 1900s after spreading from non-human primates.[1] In 2017, 36.9 million individuals worldwide were living with HIV, making the pandemic a serious public health issue. There were 1.8 million new HIV infections and 940000 deaths from AIDS-related diseases in 2017 despite the growth of antiretroviral treatment programs.[2] It was estimated that 44,000 incident HIV diagnoses occur annually in the United States (US). 25% of the estimated 1.2 million persons living with HIV in the US are women, who are most likely to receive a diagnosis during their reproductive years and account for 19% of newly confirmed cases of the virus. Approximately 8500 HIV-positive women gave birth in the US in 2014; this number has been rising over time.[3] HIV infection is one of the main causes of morbidity and mortality worldwide.[1]

From a therapeutic standpoint, pregnant women represent a unique demographic, primarily due to the possibility of preventing mother-to-child HIV transmission (MTCT) with antiretroviral medications and the have to take into account the safety of the women as well as the exposed fetuses and children.[4] HIV acquisition raises the risk of maternal morbidity and death in pregnant and breastfeeding women. It also contributes significantly—and steadily—to the global pediatric HIV infection rate.[5] Two impacts of HIV infection on the fetus include higher risk of unfavorable pregnancy outcomes and vertical transmission, both of which have a major effect on the survival of the newborn.[6] Regardless of CD4+ cell count, the World Health Organization (WHO) and UNICEF recommended in 2013 that all pregnant HIV-positive women start antiretroviral therapy (ART) early in their pregnancy and continue it for the rest of their lives.[7] The link between exposure to ART during pregnancy and unfavorable pregnancy outcomes, such as low birth weight and/or premature birth, has come to light more recently as vertical transmission rates continue to drop globally.[6,7]

According to a number of research conducted in recent years, infection-related inflammation may have a significant impact on the development of pre-eclampsia. On the other hand, preexisting data refute the notion that HIV infection contributes to the development of pre-eclampsia. In actuality, HIV-positive patients have impaired immune systems, and PE is defined by an extreme up-regulation of the overall maternal inflammatory response. Thus, it is possible to hypothesize that having HIV may reduce the risk of pre-eclampsia.[8] Pre-eclampsia is thought to be the cause of at least 42,000 maternal fatalities every year and to complicate 3–5% of pregnancies. For every pre-eclampsia-related death, at least 50–100 women have significant morbidity.[9] The brain, which can result in severe headaches, visual disturbances, or eclamptic seizures; the liver, which can cause epigastric pain or abnormal liver function tests; the kidneys, which can cause abnormal renal function tests or proteinuria; the haematological system, which can cause thrombocytopaenia, coagulopathy, or hemolysis; the lungs, which can cause low oxygen saturation or pulmonary oedema; and the placenta, which can cause fetal growth restriction, are among the organs affected by pre-eclampsia.[10,11] Over the past 20 years, several findings have suggested—contrary to other studies—that pregnant women living with HIV are less likely to develop pregnancy hypertensive problems such as PE. This study aims to determine the effect of HIV and antiretroviral therapy on the risk of pre-eclampsia.

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to make that the investigation's results are valid.

Criteria for Eligibility

For the purpose of this systematic review, we investigated the effect of human immunodeficiency virus (HIV) and antiretroviral therapy on the risk of pre-eclampsia. The main objective of this composition is to illustrate the significance of the challenges that have been recognized throughout the entire text.

To be eligible to participate in the study, researchers had to meet the following requirements: 1) The paper needs to be written in English, and it should focus on determining the effect of human immunodeficiency virus (HIV) and antiretroviral therapy on the risk of pre-eclampsia. The manuscript must fulfill both of these conditions in order to be considered for publication. 2) Several of the studies under study were released in the previous ten years. Editorials, submissions without a DOI, already published review articles, and entries that are nearly exact replicas of journal papers that have already been published are a few examples of research that are prohibited.

Search Strategy

We used "HIV"; "antiretroviral therapy"; "HAART"; "pre-eclampsia"; and "pregnant woman" as keywords. The search for studies to be included in the systematic review was carried out from February, 8th 2024 using the PubMed and ScienceDirect databases by inputting the words: "hiv"[MeSH Terms] OR "hiv"[All Fields] AND "anti retroviral agents"[Pharmacological Action] OR "anti retroviral agents"[MeSH Terms] OR ("anti retroviral"[All Fields] AND "agents"[All Fields] OR "anti retroviral agents"[All Fields] OR "antiretroviral"[All Fields] OR "antiretrovirally"[All Fields] OR "antiretrovirals"[All Fields] AND "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields] OR ("antiretroviral therapy, highly active"[MeSH Terms] OR "antiretroviral"[All Fields] AND "therapy"[All Fields] AND "highly"[All Fields] AND "active"[All Fields] OR "highly active antiretroviral therapy"[All

Fields] OR "haart"[All Fields] OR "haarts"[All Fields] AND "pre eclampsia"[MeSH Terms] OR "pre eclampsia"[All Fields] OR "pre"[All Fields] AND "eclampsia"[All Fields] OR "pre eclampsia"[All Fields] AND "pregnant women"[MeSH Terms] OR ("pregnant"[All Fields] AND "women"[All Fields] OR "pregnant women"[All Fields] OR ("pregnant"[All Fields] AND "woman"[All Fields] OR "pregnant woman"[All Fields] AND (y_10[Filter]) AND (english[Filter]) used in searching the literature.

Data retrieval

The writers conducted an analysis to ascertain whether each study met the inclusion criteria after reading the study's title and abstract. Subsequently, the authors determined which prior studies to include as references in their paper and picked those ones. This conclusion was reached after reviewing other studies that appeared to support the same pattern. All submissions must be made in English and must not have been published elsewhere.

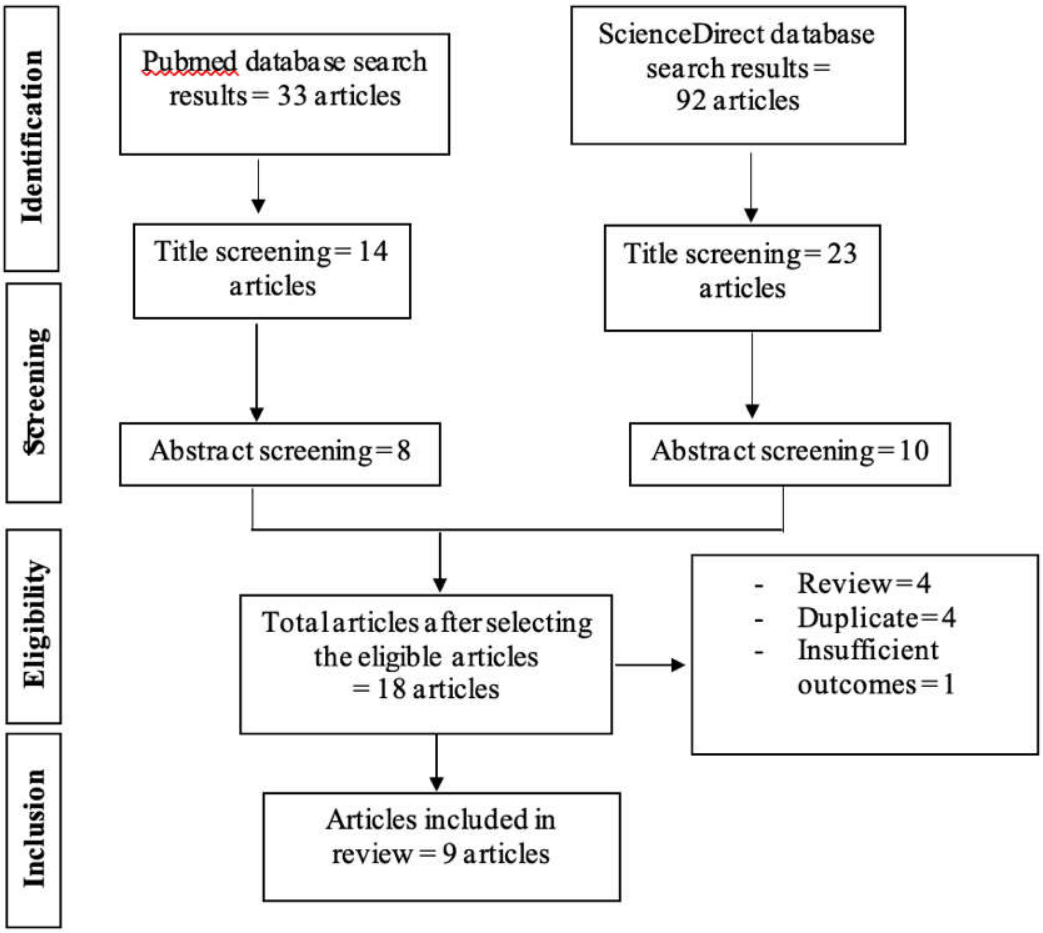

Figure 1. Article search flowchart

For the purposes of the systematic review, only papers that met all inclusion requirements were considered. By doing this, the quantity of results is whittled down to just those that are relevant to the query. The findings of any study that does not meet our standards are not taken into account. Subsequently, an extensive analysis of the research findings will be conducted. Names, authors, publication dates, locations, study activities, and parameters were among the details that came to light during the investigation conducted for this study.

Quality Assessment and Data Synthesis

Before deciding which papers to investigate further, each author conducted their own analysis of the research that was mentioned in the publication's title and abstract. The subsequent phase will involve assessing every article that meets the review's inclusion criteria and is thus appropriate for inclusion. The publications that should be included in the review will then be chosen based on the conclusions that we have found. In an effort to streamline the process as much as possible when choosing articles for evaluation, this criterion is used when choosing papers for additional assessment. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

When we searched the PubMed database, we found 33 papers, but when we searched ScienceDirect, we found 92 publications. Title screening produced a total of 14 articles for PubMed and 23 articles for ScienceDirect in the search

results. Eight papers from PubMed and ten from ScienceDirect made up the total of the papers we compiled. Four reviews, four duplicates, and one with insufficient results were all excluded. Nine studies that satisfied the requirements were finally included.

Table 1. The literatures included in this study

Author	Origin	Method	Sample Size	Result
Hall, 2014[12]	South Africa	Prospective cohort study	1093 patients with HIV (+)	The results indicated that among HIV-positive women receiving mono- or triple anti-retroviral medication, pre-eclampsia and prenatal hypertension are less common.
Imogie, 2022[13]	South Africa	Cross-sectional study	90 patients with HIV (+)	The findings indicated that hypertensive disorders of pregnancy (HDP) appear to be prevented by HIV or its treatment; however, complications from HDP may be severe in women living with HIV (WLHIV) who are getting therapy.
Lockman, 2021[14]	USA	RCT	643 patients with HIV (+)	According to the results, pregnancy complications accounted for 80 [12%] of the 643 participants, with the highest frequency of grade 3 or higher adverse events (stillbirth and preterm delivery excluded). These included gestational hypertension (17 [3%] participants, distributed similarly across the three groups) and grade 3 or higher pre-eclampsia or eclampsia (nine [1%] participants; eight in the combined dolutegravir-containing groups and one in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group).
Machado, 2015[15]	USA	Prospective cohort study	1513 patients with HIV (+)	The results of this study demonstrated that pregnant HIV-positive women who have previously experienced pre-eclampsia or eclampsia, have a BMI of ≥25, hemoconcentration with PE, and were using HAART before to conception are more likely to experience pre-eclampsia or eclampsia.

Mukosha, 2022[16]	Zambia, Africa	Retrospective cohort study	640 patients with HIV (+)	The findings of this investigation corroborate earlier findings that PE is less likely in women with HIV who are receiving treatment than in those who are not. Still, regardless of HIV exposure status, neonates born to women with PE are more likely to experience unfavorable outcomes.
Prophet, 2018[17]	USA	Retrospective cohort study	73,064 patients with HIV (+)	These findings revealed that pregnant women with sickle cell disease (SCD) had a 20% increased risk of pre-eclampsia, while those with HIV had a lower chance of pre-eclampsia. However, the likelihood of having pre-eclampsia was increased by more than 300% in those with SCD who also had HIV.
Sansone, 2016[18]	USA	Retrospective cohort study	453 patients with HIV (+)	According to this research, women who are HIV-positive are more likely to develop preeclampsia. HAART appears to be connected, at least somewhat, to this risk.
Sikhosana, 2022[19,20]	South Africa	Case-control study	571 patients with PE	The findings demonstrated a negative correlation between untreated HIV infection and preeclampsia among Black women. Despite the fact that these results suggested that untreated HIV infection protects against preeclampsia, starting treatment as soon as pregnancy is confirmed, in accordance with current national HIV management guidelines in South Africa, is still the best course of action given the risk of HIV transmission from mother to child.

Stoner, 2016	USA	Retrospective cohort study	12,813 patients with HIV (+)	According to the findings, pregnant women with untreated HIV infection were less likely than those without the virus to experience pregnancy-associated hypertension (PAH), which includes pre-eclampsia. On the other hand, the risk of PAH for HIV-positive women may rise or even return to baseline levels upon starting ART.

Hall, et al. (2014)[12] showed that there is a significant difference of the incidence of pre-eclampsia in pregnant women living with HIV. The incidences of pre-eclampsia in the HIV positive and negative groups were 35 (3.2%) and 57 (4.9%), respectively, with p value 0.045. In this study, 865 women received AZT (monotherapy) plus NVP intrapartum, 200 women had HAART (triple therapy), and in 28 cases, anti-retroviral therapy was not recorded. A CD4 count of 350 cells/mm3 is used to divide the HIV positive group according to the rates of pre-eclampsia and prenatal hypertension. Regarding this immunological status parameter, no noteworthy variations were observed. Similarly, there were no changes in pre-eclampsia (p=0.24) between the 865 women on defined monotherapy and the 200 HIV-positive women on HAART. A multiple logistic regression analysis was conducted utilizing the variables that could potentially impact the risk of pre-eclampsia, namely HIV, age, parity [0 or ≥1], smoking [yes or no], and obesity [BMI ≥30]. In pregnant women living with HIV, the risk of PE was 0.46, p = 0.002.

Imogie, et al. (2022)[13] showed that there were no differences in incidence of pre-eclampsia among WLHIV compared with HIV-uninfected women, 53 (58.9%) and 121 (57.9%), respectively. In this study, there were 209 (70%) HIV-uninfected participants and 90 (30%) WLHIV. No significant differences between primigravida women with or without HIV infection. In primigravida women with HIV negative, pre-eclampsia developed 66 103 (64%) while in pregnant WLHIV pre-eclampsia developed 20 of 27 (74%), p value 0.420. Among the WLHIV, 67.8% (61 of 90) had begun treatment before becoming pregnant, while 32.2% (29 of 90) of participants had begun antiretroviral therapy during the index pregnancy. P < 0.0001), 52 out of 61 (85%) of the latter had mean CD4 counts greater than those who started antiretroviral therapy (ART) during pregnancy (448.7 cells/mm3 versus 281 cells/mm3). Pre-eclampsia, gestational hypertension, and eclampsia categories were all developed similarly in the HIV treatment groups (pre-pregnancy or during pregnancy), with only seven women having unsuppressed VL. This was based on the level of CD4 cell count or VL. The difference in the development of these disorders was not significant (P = 0.362).

Lockman, et al. (2021)[14] showed that among 643 participants, pregnancy problems accounted for 80 [12%], with grade 3 or higher adverse events having the highest prevalence (stillbirth and premature delivery excluded). These included grade 3 or higher pre-eclampsia or eclampsia (nine [1%] participants; eight in the combined dolutegravir-containing groups and one in the efavirenz, emtricitabine, and tenofovir disoproxil fumarate group) and gestational hypertension (17 [3%] participants, distributed similarly across the three groups). Machado, et al. (2015) showed that the pregnant women living with HIV, the prevalence of PE/E was 2.3%. Furthermore, in adjusted models, having HAART at conception was associated with a PE/E (OR=2.3; 95% CI: 1.1-4.9).

Mukosha, et al. (2022)[16] showed that the prevalence of PE among women living with HIV was 4.8% (95% CI: 3.3 to 6.8) and 8.4% (95% CI: 7.3 to 9.5) among women without HIV when stratified by HIV status. The largest prevalence of HIV among women living with the virus was seen in those between the ages of 25 and 34 (16/30, 53.3%), pregnant women (17/31, 54.8%), women with parity between 2-4 (16/28, 57.1%), and unemployed women (21/31, 87.5%). The odds of PE were 50% lower in pregnant women with HIV infection on ART than in those without HIV infection (aOR 0.50; 95% CI 0.32 - 0.80; p=0.004). Prophet, et al. (2018)[17] showed that pregnant HIV-positive women were less likely to experience any kind of pre-eclampsia (OR = 0.86; 95% CI = 0.78, 0.95). Mothers with HIV alone had a decreased incidence of moderate pre-eclampsia. Moreover, mothers who were HIV-positive shared comparable risks for severe pre-eclampsia with mothers who were disease-free.

Sansone, et al. (2016)[18] showed that HIV prevalence was considerably lower in pre-eclampsia women than in the control group (24% vs. 31%, respectively; P=.014). The median CD4+ count among HIV-positive participants did not differ between cases and controls (435 cells/mL for cases and 390 cells/mL for controls; P=.563). Interestingly, only 56% of women in the normotensive control group were on triple ART, while 82% of HIV-positive women with known treatment status were in the preeclamptic group (P<.0001). Furthermore, an unadjusted odds ratio (OR) of 0.330; a 95% confidence interval (CI) of 0.197−0.552; a P-value of.001 indicated that untreated HIV infection was protective against preeclampsia. Sikhosana, es al. (2022)[19] showed that the prevalence of HIV was significantly lower in women with preeclampsia than in women in the control group (24% vs 31%, respectively; P=.014). There were 56% of women in the normotensive

control group were on triple ART, while 82% of women with HIV and known treatment status were in the pre-eclampsia group (P<.0001).

Stoner, et al. (2016)[20] showed that women with HIV infection who were untreated or given prophylaxis had a lower likelihood of pregnancy-associated hypertension (PAH) than did women without HIV infection (106 (2.1%) or 545 (10.6%) vs. 4,115 (80.2%)), whereas women with HIV infection given ART had similar odds to women without the infection 362 (7.1%) in unadjusted models, p = <0.001. Compared to women who were HIV-negative, those on ART showed noticeably higher risks of developing PAH in multivariable analysis. The chances were still lower for HIV-positive women who were not on antiretroviral therapy.
Parity, BMI, numerous pregnancies, and antiretroviral therapy were linked to PAH in HIV-positive women. Compared to women who were not receiving treatment or who were only receiving prophylaxis, the odds of PAH in women undergoing ART were 1.27 times greater. PAH was unrelated to the most recent CD4 count. The odds of PAH were identical for women who started treatment during pregnancy compared to those who started treatment prior to pregnancy, according to multivariable analysis.

DISCUSSION

The purpose of this research was to review studies published after January of 2014 and up to February of 2024 that investigated the effect of HIV and antiretroviral therapy on the risk of pre-eclampsia. Pre-eclampsia is a pregnancy-specific illness that affects 3–17% of pregnancies globally. It is the main factor contributing to morbidity and mortality in both mothers and newborns.[23] Elevated blood pressure, defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, along with proteinuria (>300 mg/24 h) in a previously normotensive woman are the clinical manifestations of pre-eclampsia.[10,11]

Seven of our identified studies suggested that HIV infection or untreated HIV infection and antiretroviral therapy or HAART can lower PE risks. Nevertheless, additional research revealed that HIV infection may raise the risk of PE. These findings contrasted with those of a prior study, which found no correlation between the likelihood of having PE and HIV infections, whether treated or not (RR, 1.04; 95%CI, 0.89–1.21).[8] Our findings, however, are in line with the research of Calvert and Ronsmans, which found a strong correlation (RR,1.46; 95% CI, 1.03–2.05) between HIV and hypertensive problems during pregnancy.[21] The mechanism underlies HIV infection's protective effects is unknown. It may be linked to immunological suppression in women living with HIV, as our hypothesis suggests.[22]

While our research indicates that untreated HIV infection during pregnancy may lower the risk of pre-eclampsia, untreated HIV infection during pregnancy was also linked to a higher risk of several unfavorable birth outcomes, such as preterm birth, low birthweight, small-for-gestational-age babies born, and stillbirth, with women with advanced HIV disease or immunosuppression having the highest risk.[4] ART is the universally accepted standard of therapy for PMTCT and to address the immunological incompetence associated with HIV-1 infection. As antiretroviral therapy (ART) boosts immunological function in HIV-1-positive people, pregnant women on ART may have a serious risk of severe comorbidity with PE. Numerous studies demonstrate how ART affects decidualization and placentation, resulting in endothelial dysfunction in the mother and the hypertensive signature of PE.[23]

The increased risk of preterm births in HIV-positive women has been linked to the use of HARRT, specifically the protease inhibitors (PI) components of anti-retroviral therapy. However, some studies did not find that the association was dependent on protease inhibitors. There was no general correlation found between treatment and preterm risk in a meta-analysis that particularly looked at research examining anti-retroviral therapy during pregnancy and the risk of premature delivery.[3] By enabling NK cells to release CC-chemokines, which inhibit endogenous HIV-1 replication through non-cytolytic pathways, highly active antiretroviral therapy (HAART) reduces HIV-1 viremia [84]. Nevertheless, this is detrimental during pregnancy because NK cell activation can cause trophoblast invasion dysregulation and persistent immunological activation, both of which are linked to the development of PE.[24]

CONCLUSION

This systematic review found that maternal HIV infection and not using antiretroviral therapy reduced the risk of PE. However, further investigations with more well-designed studies with larger sample sizes are still needed.

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