

HAART-associated risk of preeclampsia in HIV+ women

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Abstract

Background: Until the advent of highly active antiretroviral therapy (HAART) in 1996, HIV infections were considered a death sentence. In 2013, an estimated 1,400,000 million pregnant women were living with HIV globally, all of whom were at risk of mother-to-child-transmission. Thankfully, many women have access to HAART, the gold standard treatment. However, there are concerns about risks of pregnancy complications associated with HAART, such as preeclampsia, characterized by high blood pressure and proteinuria.

Objectives: To conduct a structured literature review to determine whether there is a relationship between HAART and preeclampsia in HIV+ women, and implications for women in southern Africa.

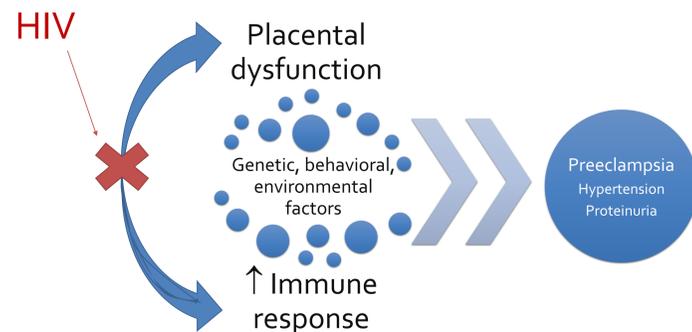
Methods: Five major databases were searched using a comprehensive search strategy of appropriate keywords, variations, and MeSH terms. The database search generated 106 publications, reduced to 35 after removing duplicates. Titles and abstracts were screened for relevance, and remaining publications were read in full. Seven studies that met inclusion criteria were critically appraised using appropriate CASP checklists for risk of bias. Sample size, target population, study design, interventions, outcomes, and raw data were extracted.

Results: Seven publications were included in final analysis, with mixed results. Some show an increased risk of preeclampsia in women receiving HAART, while others show decreased risk.

Conclusion: There is little consensus in the literature about the relationship between HAART and preeclampsia. Further research is needed in order to protect HIV+ women from severe outcomes during pregnancy while still preventing mother-to-child transmission, especially for women in developing countries with limited access to essential obstetric care and HIV treatment.

Background

- 1,400,000 pregnant women living with HIV worldwide¹²
- HIV during pregnancy is associated with adverse maternal and fetal outcomes such as preterm birth, low birth weight, maternal and fetal death
- Interestingly, HIV is associated with a reduction in preeclampsia and other hypertensive disorders^{5,7,9}
- Preeclampsia is a serious complication of pregnancy that is a major cause of maternal death in developing countries¹¹



- Highly active antiretroviral therapy (HAART) is a combination treatment of three or more antiretroviral medications¹⁰
- HAART is very effective at preventing mother-to-child transmission of HIV¹
- HAART may work to restore immune function in pregnant HIV+ women, thereby restoring the risk of preeclampsia⁴

Research Question

Is there an association between highly active antiretroviral therapy and preeclampsia in HIV-positive pregnant women?

Methods

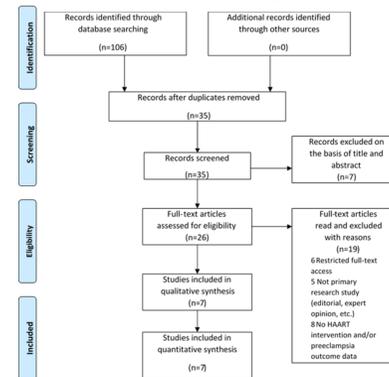
A structured literature review was conducted to determine whether there is a relationship between highly active antiretroviral therapy (HAART) and preeclampsia in HIV positive women, and to examine possible implications of a relationship for women in developing countries.

Five major databases (MEDLINE, PubMed, Embase, Cochrane Central, and DARE) were searched using a predetermined search strategy (Figure 1.) on March 18th, 2015. A flow diagram adapted from the PRISMA 2009 Flow Diagram⁵ was used to record the selection and screening process of articles included for review (Figure 2.).

Figure 1. Search strategy example from MEDLINE. Same strategy was used for other databases without MeSH terms.

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Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
1 Pre-Eclampsia/
2 (preeclamp* or pre-eclamp*).ti,ab.
3 or/1-2
4 Antiretroviral Therapy, Highly Active/
5 HAART.ti,ab.
6 (antiretroviral or anti-retroviral).ti,ab.
7 exp Anti-Retroviral Agents/
8 anti-hiv.ti,ab.
9 or/4-8
10 3 and 9
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Figure 2. Flowchart of study identification. Diagram adapted from the PRISMA Flow Diagram⁵.



Inclusion criteria: 1) population had to include HIV-infected pregnant women. 2) Systematic reviews, meta-analyses, RCT, cohort, or case-control study. 3) HAART as primary intervention or included as factor in analysis. 4) Preeclampsia as primary outcome or ancillary outcome. 5) Raw data had to be available for extraction.

Data extraction: study design, sample size, primary interventions and outcomes, and raw outcome data used to calculate relative risk or incidence rate (Table 1.).

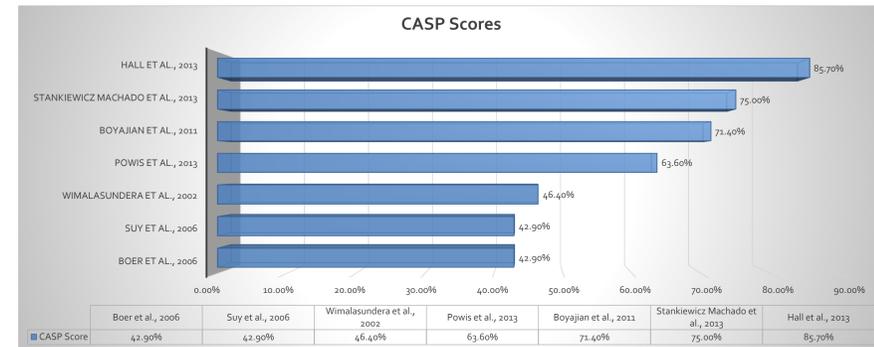
Risk of bias assessment: CASP checklists for randomized controlled trials and cohort studies⁷ were used to evaluate three major sources of bias: selection bias, measurement/classification bias, and confounding bias. The RCT scored out of 11 and cohort studies out of 14 (Figure 3.).

Results

Table 1. Data extracted from studies included for review

Study, study design, sample size	PICO	Association?
Boer et al., 2006 Cohort study N=339	Population: Pregnant women; Amsterdam and Rotterdam, the Netherlands Primary intervention: HAART Comparison: HIV- women Primary outcomes: MTCT, preterm delivery, low birthweight, preeclampsia Data analysis: Incidence of PE with HAART = 2.8%; among controls (given) = 1.0%	May exist
Boyajian et al., 2011 Cohort study N=364	Population: Pregnant women; Toronto, ON Primary intervention: HAART Comparison: HIV- women Primary outcome: Preeclampsia Data analysis: RR = 0.64	HAART may be a weak protective factor
Hall et al., 2013 Cohort study N=2266	Population: Pregnant women; South Africa Primary intervention: HAART Comparison: HIV- women Primary outcome: Preeclampsia Data analysis: RR = 0.70	HAART may be a weak protective factor
Powis et al., 2013 RCT N=733	Population: HIV+, HAART-naïve pregnant women; Botswana Primary intervention: Viral load as a result of select HAART combinations Comparison: 3 different HAART combinations: TZV, CBV-KAL, and CBV-nevirapi Primary outcome: Preeclampsia Data analysis: Incidence = 1.5%; however no non-HAART comparison	Unclear
Stankiewicz Machado et al., 2013 Cohort study N=1513	Population: Pregnant women; Latin America and the Caribbean Primary intervention: HIV-infection; HAART analyzed as a risk factor Comparison: Physiological, socioeconomic, and other risk factors Primary outcome: Pregnancy induced hypertension, preeclampsia, and eclampsia Data analysis: RR = 2.10	Yes, association exists
Suy et al., 2006 Cohort study N=8768	Population: Pregnant women; Barcelona, Spain Primary intervention: HAART Comparison: HIV- women and data on HIV+ women prior to the advent of HAART Primary outcome: Preeclampsia Data analysis: RR = 1.5	Yes, association exists
Wimalasundera et al., 2002 Cohort study N=428	Population: Pregnant women; London, England Primary intervention: HAART Comparison: HIV- women and data on untreated HIV+ women before HAART Primary outcome: preeclampsia Data analysis: RR = 1.5	Yes, very strong association

Figure 3. Data table and graph illustrating CASP assessment of risk bias scores. Percentage indicates criteria that were met to reduce risk of bias.



Discussion

The majority of the studies with low CASP scores were North American and European, and were published much earlier. Three studies were done in developing regions^{4,6,8}. **Selection bias:** partially unavoidable; comparison groups were systematically different. Socioeconomic status was accounted for in only one study⁸. HIV+ women in this review may not be representative of all HIV+ pregnant women.

Measurement/classification bias: most studies relied on data from medical charts. **Confounding bias:** HIV+ women are less likely to have certain comorbidities. Therefore, differences in preeclampsia between HIV+ and HIV- women may be underestimated.

Limitations: search strategy. Did not specify comparisons. The review could be improved with a search through the reference lists of included studies. A more comprehensive tool for evaluating risk of bias would improve overall strength of the review.

Strengths: the research question generated relevant sources and identified important issues, which leads to another strength: this review identified gaps in the literature. There may not be enough evidence here to support a relationship between HAART and preeclampsia, but there is not enough to deny one, either.

Conclusions

The literature collected in this structured review does not provide sufficient evidence to formulate a concrete conclusion. However, it does well in identifying gaps in the literature and informing future research. All studies agreed that benefits of HAART in preventing MTCT of HIV far outweigh potential risk of preeclampsia associated with HAART, and that a restorative effect of HAART on the immune system may restore risk of preeclampsia to HIV- baseline risk. More research is necessary to further elucidate associations between HAART and preeclampsia.

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