HIV, Antiretroviral Therapy, and Hypertensive Disorders in Pregnancy: A Systematic Review and Meta-analysis

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Background: There are data to suggest that infection with HIV or use of highly active antiretroviral therapy increases the risk of hypertensive disorders in pregnancy. This systematic review and meta-analysis aims to provide an overview of the research hitherto.

Methods: A systematic review of EMBASE, PubMed, and The Cochrane Library databases was conducted to obtain articles about the association between HIV in pregnancy and/or HIV therapy and the risk of developing pregnancy-induced hypertension (PIH), pre-eclampsia, eclampsia, or Hemolysis Elevated Liver enzymes Low Platelet count syndrome. Quality of articles was evaluated with an adapted Cochrane Collaboration bias assessment tool. Relative risks (RRs) were pooled with a random-effects meta-analysis weighted by the inverse of their variance.

Results: Of the 2136 articles screened, 28 studies were eligible for inclusion; 15 studies reported on the association with PIH, 16 on pre-eclampsia, 5 on eclampsia, and 3 articles on HIV therapy regimens. All articles had a high risk of bias, and between-study heterogeneity was considerable. Based on the meta-analysis, there does not seem to be an association between HIV and PIH [RR 1.26, 95% confidence interval (CI): 0.87 to 1.83, I^2 = 78.6%], pre-eclampsia (RR 1.01, 95% CI: 0.87 to 1.18, I^2 = 63.9%), or eclampsia (RR 1.61, 95% CI: 0.14 to 18.68, I^2 = 97.0%). A meta-analysis of the association with HIV therapy and risk of hypertensive disorders in pregnancy could not be performed.

Conclusions: This meta-analysis shows no significant association between HIV positivity and PIH, pre-eclampsia, or eclampsia. However, the high risk of bias within most studies limits the strength of conclusions and well-designed studies are necessary to confirm or refute these findings.

Key Words: eclampsia, HAART, HIV, pre-eclampsia, pregnancy-induced hypertension

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INTRODUCTION

In 2012, 35.3 million people were globally infected with HIV. More than half of this population consisted of women and girls of reproductive age.[1] HIV has been linked to several adverse perinatal outcomes, including postpartum hemorrhage,[2] puerperal sepsis,[3–6] intrauterine growth restriction,[7,8] low-birth weight,[7,9–12] preterm birth,[7,8,13,14] and mortality[15]; however, findings about the direction and strength of the relationships are inconsistent.

Hypertensive disorders in pregnancy, including pregnancy-induced hypertension (PIH), pre-eclampsia, eclampsia, and Hemolysis Elevated Liver enzymes Low Platelet count (HELLP) syndrome, are among the leading causes of maternal morbidity and mortality worldwide.[16,17] Although the exact pathophysiology of hypertensive disorders in pregnancy remains unclear,[18] deficient placental implantation early in pregnancy, cardiovascular and/or immunologic maladaptation to pregnancy, and enhanced systemic inflammatory reaction may be involved.[19] Because HIV has immune-depressive effects, an association between pre-eclampsia and HIV has been suggested.[20] The association between HIV and hypertensive disorders in pregnancy can be hypothesized to either increase or decrease the risk. Physiologic pregnancy is an immunomodulated state that induces fetal tolerance, without compromising the reactive immunity against invading pathogens through regulatory T cells.[21] Pre-eclampsia could result from poor placentation-induced oxidative and endoplasmic reticulum stress, resulting in generalized endothelial dysfunction with immune activation, vascular reactivity, decreased intravascular volume, and the clinical syndrome.[22] The immunodepressive effects of HIV could reduce the hyperinflammation associated with

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pre-eclampsia.[23] In contrast, an increased risk for pre-eclampsia could be postulated to arise from chronic aterial dysfunction with endothelial damage, which has been previously associated with HIV.[24] A previous meta-analysis reported an increased risk of PIH associated with HIV, whereas no association between HIV and pre-eclampsia, and eclampsia, was reported.[2] Additional studies were recently published that assessed the association between HIV and hypertensive disorders in pregnancy. Highly active antiretroviral therapy (HAART) is indicated in HIV patients with low CD4 T-cell count and in prevention of vertical transmission from the mother to the child. It has been advocated since 1996, and its success is reflected in globally reduced vertical transmission rates dropping from 25%–30% to <1%.[25–29] Risks of adverse events for both the baby and the mother seem low on short term, but there has not been a systematic review regarding risk of developing hypertensive disorders in pregnancy among HAART recipients. HAART could possibly influence the postulated inhibitory effect of HIV on the development of any of the hypertensive disorders during pregnancy. In addition, the described endothelial toxicity and vascular dysfunction caused by HAART makes these patients more prone to developing hypertensive disorders.[30,31]

OBJECTIVE

To resolve the inconsistency in the published results, we conducted a systematic review and meta-analysis of all available data to estimate the association between HIV and hypertensive disorders in pregnancy. In addition, we assessed the association between HAART treatment and hypertensive disorders in pregnancy.

METHODS

Search Strategy and Eligibility Criteria

This systematic review was based on the guidelines provided by PRISMA[32] and registered in the PROSPERO review registry for systematic reviews (ID: CRD42014009529[33]).

The search was performed in three electronic bibliographic databases: PubMed/MEDLINE, The Cochrane Library (Cochrane Database of Systematic Reviews), and EMBASE for all publications up to April 2014, using a combined text and MeSH search strategy and terms related to pregnancy, hypertensive disorders in pregnancy, PIH, pre-eclampsia, eclampsia and HELLP syndrome, HIV/AIDS, and HAART treatments including various regiment options. The search terms are available in Supplemental Digital Content A, (http://links.lww.com/QAI/A686). Reference lists of included articles were screened for additional relevant articles. Articles were included if they had described the association between HIV or HAART and hypertensive disorders in pregnancy. There was no restriction based on year of publication, study design, type of facility, geographical location, language, or time of follow-up. Titles and abstracts were screened by 2 independent reviewers according to predefined inclusion and exclusion criteria. Any discrepancies were discussed and resolved by full-text evaluation. Animal, biomolecular, or genetic studies, case reports, conference abstracts, reports of proceeding, or oral presentations were excluded. When results were published multiple times, the data were used only once from the most completely reporting article. In case of incomplete data or unavailable full-text articles, the corresponding author was contacted by e-mail if possible.

Data Extraction

Using a standardized data extraction form, data on study design, study setting, country, population (age and parity), number of patients included, number of controlled, HAART treatment at the moment of inclusion, incidences of hypertensive disorders in pregnancy in HIV positive and/or HAART recipients and control groups, risk estimates, and follow-up were extracted. If relative risk (RR) was not provided, this was calculated with its 95% confidence interval (95% CI), using SPSS version 20.0 software (IBM Corp., Armonk, NY).[34] Extraction was performed by a single reviewer who was not blinded for journal or author details. A second reviewer was available in case more clarity was needed.

Quality Assessment

Quality of the selected articles was assessed at study level, using an adapted version of the Cochrane Collaboration tool also used in comparable reviews.[2,35] Studies were scored on completeness of data, origin of the data (measurements performed by authors or database research), the presence of a clear definition of (or reference to) the outcomes, and whether and which confounders were taken into account (matching between cases and controls, logistic regression analysis). Bias risk was assigned as low risk, high risk, or unclear, according to the quality assessment tool in Supplemental Digital Content D (http://links.lww.com/QAI/A686).

Statistical Analyses

Random-effects meta-analyses used to obtain pooled estimates were derived from study-specific log-transformed RRs or equivalents and the 95% CI for women with and without HIV and risk for development of PIH, pre-eclampsia, or eclampsia. Studies were weighted based on the inverse of the variance of the log RR based as the estimate of statistical size. Sensitivity analyses were performed for geographical region (by continent), study design (prospective or retrospective), and year of publication (before or after 2004). The I^2 statistic was used to assess between-study heterogeneity. Publication bias was assessed with funnel plots and tested with Egger test for funnel plot asymmetry, if there were more than 10 articles available for an outcome. All statistical analyses were performed with Stata (version 11.0, StataCorp, College Station, TX).[36]

RESULTS

The systematic search identified 2136 articles, of which 78 articles remained after title and abstract screening (Fig. 1). Seventy-three of these were available in full text. Of these, 19

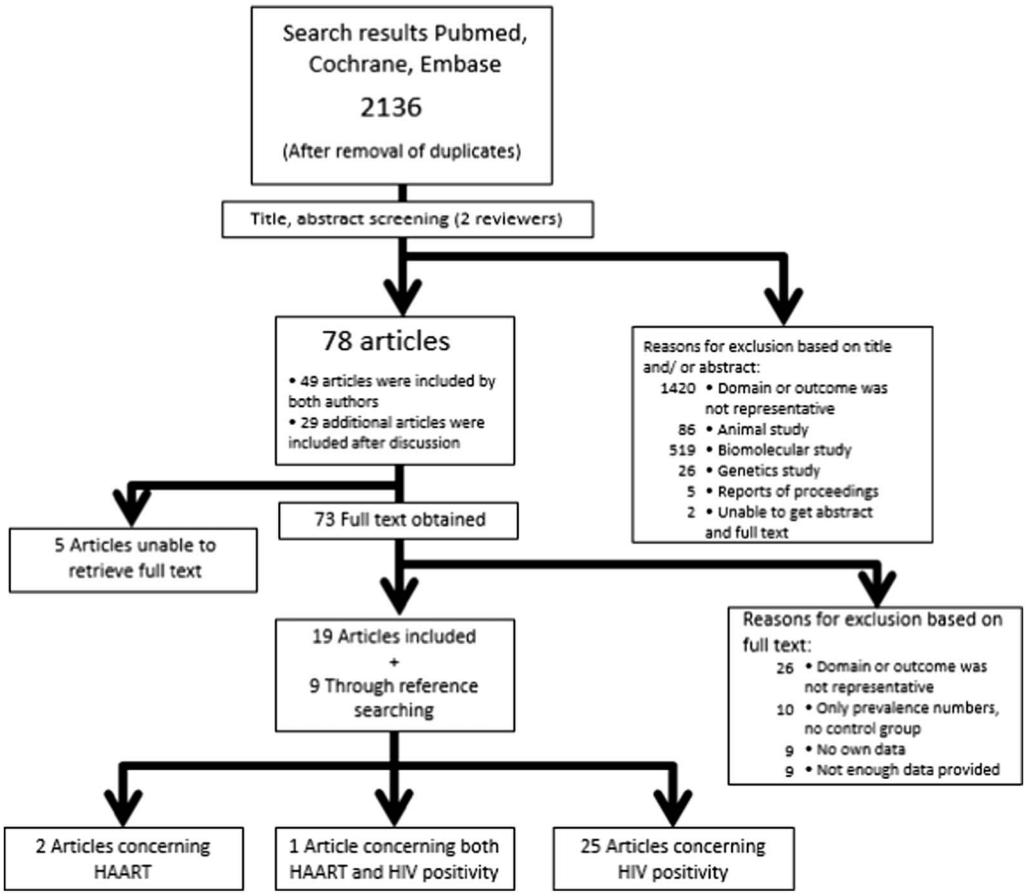

FIGURE 1. Flowchart of the process of article selection for systematic review.

articles contained relevant information. Nine additional articles were not retrieved by our original search because they were not indexed in the searched databases and added after reference checking. As a result, a total of 30 data sets were included in this review.

Table S1 (see Supplemental Digital Content B, http://links.lww.com/QAI/A686) provides an overview of study characteristics. Studies were published over a 25-year time period (1989–2014) and reported on between 31 and 6235 HIV participants. Fifteen studies were on PIH,[3,8,20,37–48] 16 on pre-eclampsia,[4,13,20,37,42–44,49–57] 5 on eclampsia,[38,42,43,45,53] and three on HAART and its association with hypertensive disorders in pregnancy.[28,57,58] Two articles[4,37] reported on the same database, and the almost complete study[4] was included in the meta-analysis. No interventional studies were identified, 1 case–control study was included and the other studies were either prospective (48%) or retrospective (52%) cohort studies. Of the included studies, 39% had study populations from sub-Saharan African countries, 21% originated from North America, 18% came from South America, 11% consisted of data from Europe, and 11% from Asia (India).

Bias Assessment

The overall risk assessment is summarized in Figure 2 (a more detailed overview of each domain of bias is available in Supplemental Digital Content E, http://links.lww.com/QAI/A686). Overall, quality of the studies was low with a high proportion of studies displaying a high risk of bias or unclear risk of bias on the 5 reported domains. Confounders were only taken into account and reported by 19% of the studies. Half of the studies did not report a clear definition of outcome. The studies that did define a study outcome differed in outcome definition or were incomplete. In most studies, medical records were used as a source of data. Most studies did not report on missing data. The funnel plots for PIH and pre-eclampsia showed on visual inspection some evidence of publication bias in smaller studies, although Egger test was not significant (PIH: $P = 0.70$, pre-eclampsia: $P = 0.24$). For eclampsia, no funnel was plotted because of the low number of studies included (see Supplemental Digital Content F1-2, http://links.lww.com/QAI/A686).

HIV and Hypertensive Disorders in Pregnancy

Fifteen studies evaluated the association between HIV and PIH (Suppl. B—Table 1, http://links.lww.com/QAI/A686) and reported on between 44–6235 HIV patients and 88–4,501,420 controls (HIV+ total: n = 11,998, median = 212; HIV− total: n = 4,539,012, median = 302). The incidence of PIH ranged from 1% to 17%. Three studies found that HIV positive women had an increased risk of

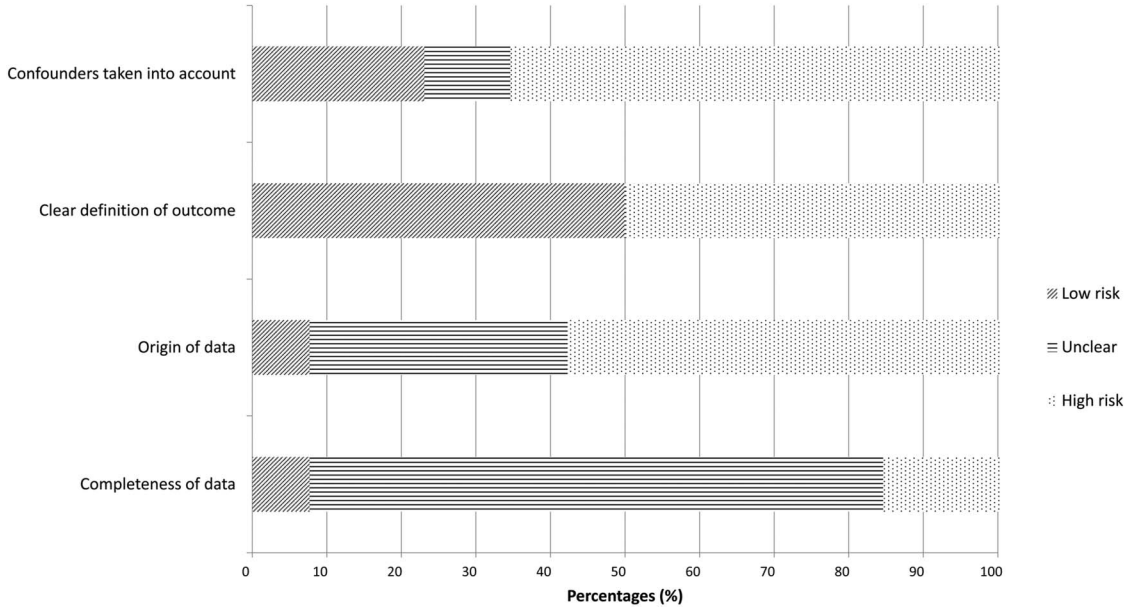

FIGURE 2. Results of bias evaluation for included studies (for full assessment, see Supplemental Digital Content E, http://links.lww.com/QAI/A686).

PIH,[40,45,48] one article reported a decreased risk of HIV,[20] and the remaining articles did not observe a significant effect, although 7 showed a trend toward a decreased risk. The pooled analysis did not find an association between HIV and PIH (RR = 1.26, 95% CI: 0.87 to 1.83); the I^2 of 78.6% suggested considerable heterogeneity between studies (Fig. 3A).

Sixteen studies examined the association between HIV and pre-eclampsia (Suppl. B—table 1, http://links.lww.com/QAI/A686) and included between 31–6235 HIV+ participants and 42–4,501,420 HIV− controls (HIV+ total: n = 16,564, median = 133; HIV− total: n = 8,800,820, median = 288). The incidence of pre-eclampsia in study populations ranged between 0.8% and 43%. Fifteen articles did not find a significant association. The two remaining articles were contradictory: Mattar et al[51] found an RR of 0.08 (95% CI: 0.01 to 0.54) of pre-eclampsia in HIV positive women (n = 123) in Brazil who received mono or combined therapy compared with HIV negative control women. In contrast, Suy et al[55] observed a risk ratio of 3.84 (95% CI: 2.05 to 7.21) in Spain. The meta-analysis did not show an association (RR = 1.01, 95% CI: 0.87 to 1.18) and had substantial heterogeneity (I^2 = 63.9%) (Fig. 3B).

Five studies reported on the association between HIV and eclampsia and included between 31–704 HIV patients and 42–23,377 controls (HIV+ total: n = 1137, median = 109; HIV− total: n = 25,486, median = 170). Two reported an increased risk, the other three a reduced risk. The corresponding meta-analysis showed no significant association with a large CI (RR = 1.61, 95% CI: 0.14 to 18.68) and high heterogeneity (I^2 = 97.0%) (Fig. 3C).

Sensitivity analysis for PIH and pre-eclampsia shows no clear difference for prospective and retrospective study or by year of publication. The only outlier in the regional stratification was a study published in the United States by Haeri et al[44] among HAART-receiving HIV+ patients showing a reduced risk of PIH [n = 151, controls: n = 302, RR = 0.16 (0.02–1.17)]. For the pre-eclampsia data sets, the only outlier by region was a Brazilian study by Mattar et al.[51]

HAART and Pregnancy-Related Hypertensive Disorders

Three articles described the incidence of hypertensive disorders in women receiving HAART regimens (see Supplemental Digital Content C: Table S2, http://links.lww.com/QAI/A686). Bera[58] did not include a reference group to compare their incidence of 7.5% pre-eclampsia with. Shapiro et al[28] did not find a difference in PIH incidence for three different HAART regiments (nucleoside reverse-transcriptase inhibitors and protease inhibitors) compared with standard of care (nevirapine, lamivudine, and zidovudine). The Wimalasundera et al[57] study was the only study that compared a HIV negative group to a HIV positive group receiving triple antiretroviral therapy, and no difference in pre-eclampsia incidence was observed. A meta-analysis of the association between HAART and any of the hypertensive disorders in pregnancy was not possible.

DISCUSSION

Our systematic review and meta-analysis shows no clear association between HIV and hypertensive disorders in pregnancy. However, caution must be taken when drawing conclusions from these results as the available evidence is of low quality with a high risk of bias. Therefore, the most pertinent conclusion would be to call for a well-designed study with defined outcome measures, full reporting on the completeness of data and the consideration of confounders. This should also include the effect of HAART treatment on

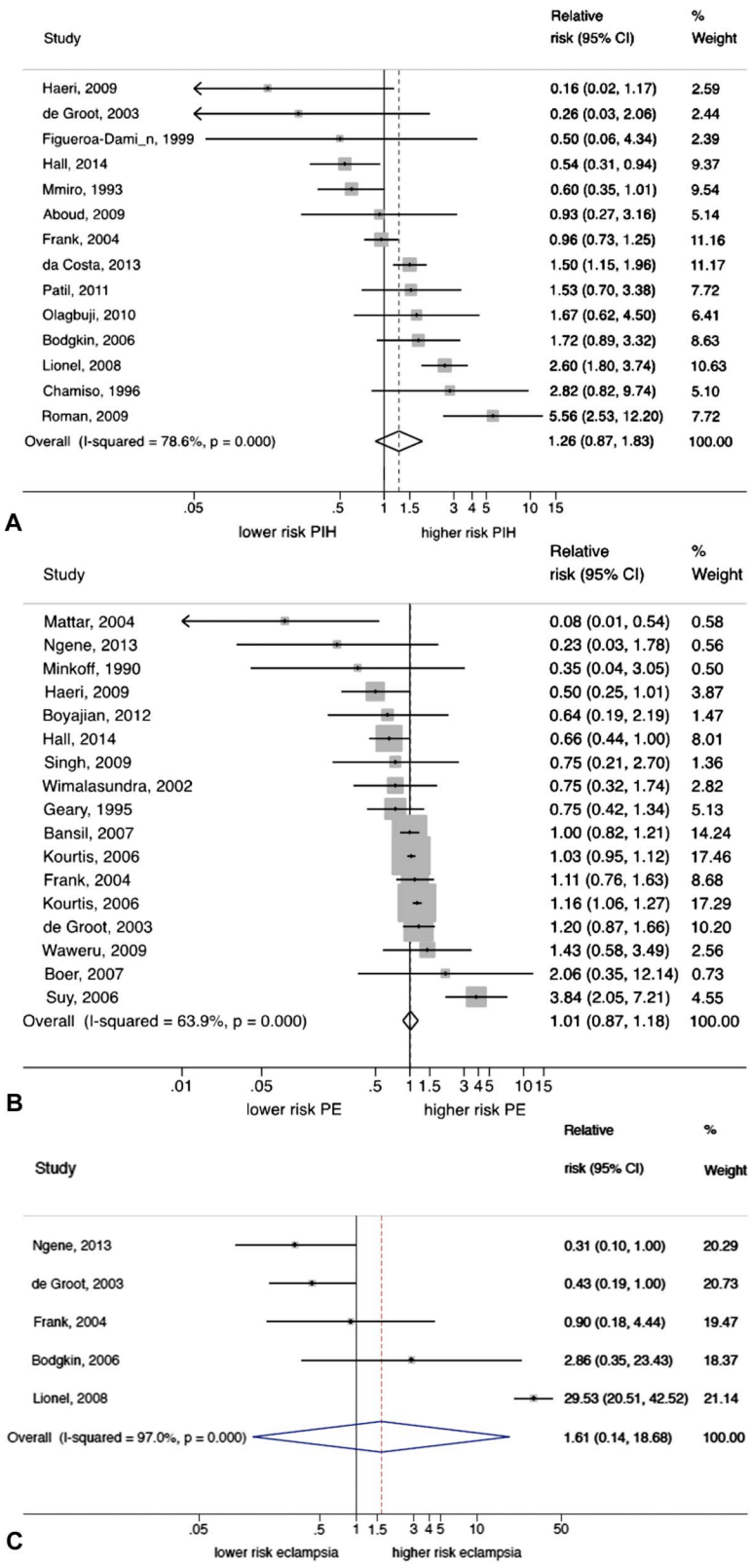

FIGURE 3. A, Meta-analysis of the association between HIV and risk of developing PIH (n = 14). B, Meta-analysis of the association between HIV and risk of developing pre-eclampsia (n = 17). C, Meta-analysis of the association between HIV and risk of developing eclampsia (n = 5).

the risk to develop any of these disorders. A further reason to assess the risk of hypertensive disorders during pregnancy in women receiving HAART are the side effects associated with this therapy such as thrombocytopenia and elevated liver enzymes. These are defining criteria of pre-eclampsia in absence of proteinuria and may result in misdiagnosis of women, with all obstetric consequences associated.[59,60] The only study that assessed pre-eclampsia incidence before and after initiation of HAART did not observe a difference in pre-eclampsia incidence.[4]

Our results contradict with the meta-analysis by Calvert and Ronsmans[2] who reported an association between HIV and with PIH with a RR of 1.46 (95% CI: 1.03 to 2.05). This difference may be attributable to the inclusion of 5 recently published additional articles that do not observe an increased risk. As pre-eclampsia and eclampsia are the more narrowly defined severe disorders on the hypertensive spectrum, the authors pointed out that a difference in risk for PIH and pre-eclampsia or eclampsia is more likely to be attributable to measurement errors and high risk of bias than underlying biological mechanisms.

A strength of our systematic review is that we included all available literature from the 3 major databases, resulting in global representation of the data. One study not included in the meta-analysis but relevant for the scope of this question was the Kalumba et al[61] study. The authors followed a different approach to investigate the association between HIV and pre-eclampsia, comparing HIV rates in pre-eclamptic and normotensive women, thus reversing domain and outcome. Study results showed a lower incidence in the

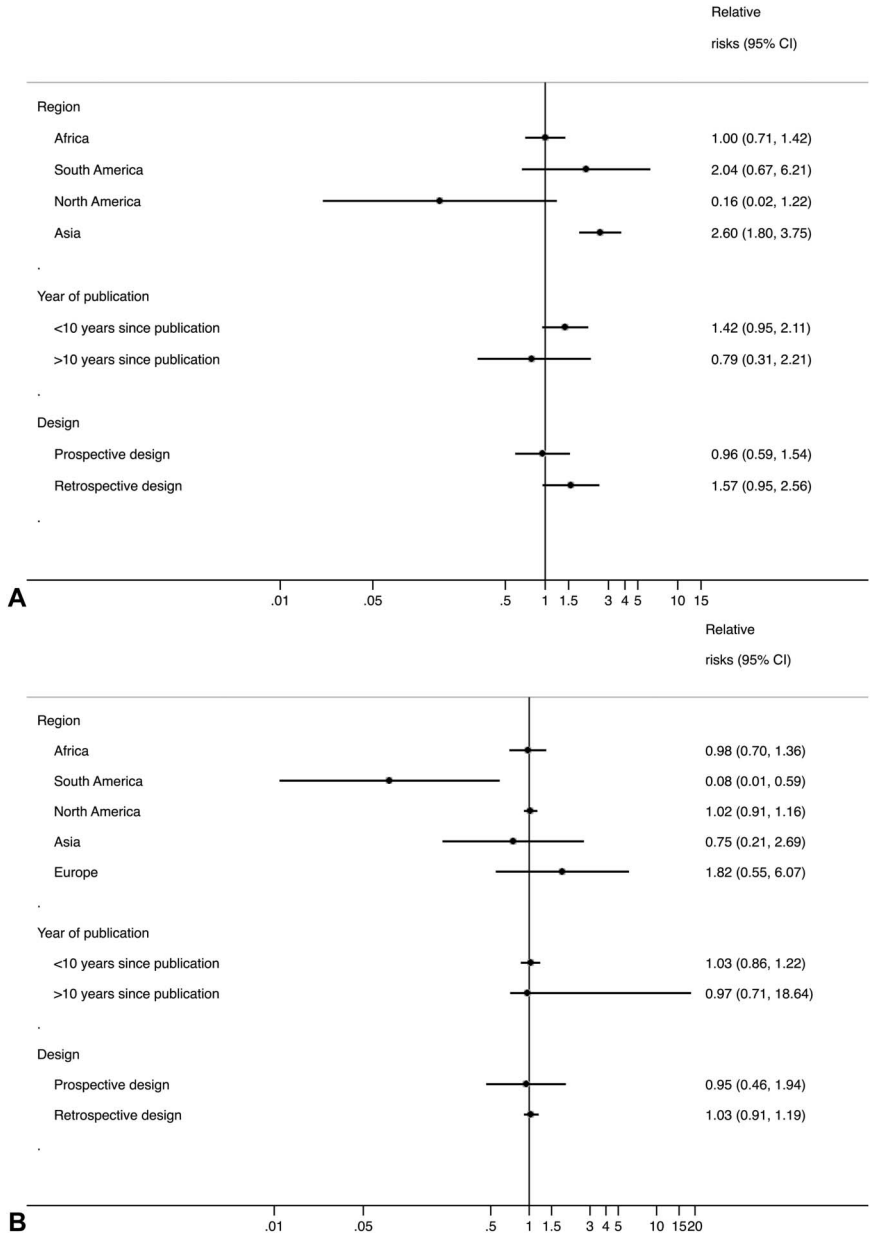

FIGURE 4. A, Sensitivity analyses for PIH. B, Sensitivity analyses for pre-eclampsia.

pre-eclampsia group of HIV (odds ratio = 0.62, 95% CI: 0.47 to 0.82). However, close monitoring of HIV positive women during pregnancy may result in optimized management of risk factors or prevention of progression of PIH to pre-eclampsia, and therefore a study in which the included women receive the same standard of care irrespective of HIV study would be more optimal. Heterogeneity in levels of care of the included studies may also be reflected in the observed widespread of event rate, with high-risk obstetric patients more often attending tertiary level or specialized facilities.

Limitations of this study are inherent to the high risk of bias of individual studies included in the review and meta-analysis. Only a few studies controlled for possible confounders. Possibly diagnostic or measurement errors were likely introduced as a result of the source of data used and lack of disease definition. A further limitation is introduced in the qualification of severity of HIV other than recipient of HAART treatment, for example, by CD4 count as an indicator of immune competence. In fact, it has been suggested that women with a high viral load before initiating HAART treatment are at an increased risk for preeclampsia.[62]

Women with HIV are 8 times more likely not to survive their pregnancy or the postpartum period compared with HIV unaffected women.[63] Therefore, the clinical impact of a question that can improve the antenatal care provided to pregnant HIV patients is significant. Given the increasing availability of HAART treatment, understanding the risk of women to develop hypertensive disorders in pregnancy could improve guidelines about the initiation of prevention strategies such as low-dose aspirin[64,65] and calcium supplementation.[66] Importantly, reducing mortality in HIV infected pregnant women requires not only a focus on direct obstetric causes such as sepsis and endometritis.[2] As mortality is also largely contributable to non–pregnancy-related factors, including meningitis, pneumonia and tuberculosis, and anemia,[67] there should be an integrated strategy for mortality reduction.

CONCLUSIONS

This systematic review and meta-analysis shows no significant association between HIV positivity and PIH, pre-eclampsia, or eclampsia. However, the high risk of bias within most studies limits the strength of conclusions and well-designed studies are necessary to confirm or refute these findings.

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