

The contribution of hiv to pregnancy-related mortality: a systematic review and meta-analysis

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Objectives: Whilst much is known about the contribution of HIV to adult mortality, remarkably little is known about the mortality attributable to HIV during pregnancy. In this paper we estimate the proportion of pregnancy-related deaths attributable to HIV based on empirical data from a systematic review of the strength of association between HIV and pregnancy-related mortality.

Methods: Studies comparing mortality during pregnancy and the postpartum in HIV-infected and uninfected women were included. Summary estimates of the relative and attributable risks for the association between HIV and pregnancy-related mortality were calculated through meta-analyses. Varying estimates of HIV prevalence were used to predict the impact of the HIV epidemic on pregnancy-related mortality at the population level.

Results: 23 studies were included (17 from sub-Saharan Africa). Meta-analysis of the risk ratios (RR) indicated that HIV-infected women had eight times the risk of a pregnancy-related death compared with HIV-uninfected women (pooled RR: 7.74, 95% CI 5.37–11.16). The excess mortality attributable to HIV among HIV-infected pregnant and postpartum women was 994 per 100,000 pregnant women. We predict that 12% of all deaths during pregnancy and up to one year postpartum are attributable to HIV/AIDS in regions with a prevalence of HIV among pregnant women of 2%. This figure rises to 50% in regions with a prevalence of 15%.

Conclusion: The substantial excess of pregnancy-related mortality associated with HIV highlights the importance of integrating HIV and reproductive health services in areas of high HIV prevalence and pregnancy-related mortality.

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Introduction

Amongst women of reproductive age, HIV/AIDS is the leading cause of death [1] and women in sub-Saharan Africa also experience the highest levels of maternal mortality [2]. How HIV interacts with pregnancy is still a matter of debate. Some have argued that pregnancy may accelerate HIV progression or that the risk of obstetric complications may be increased in HIV-infected women, but the available evidence in support of either of these hypotheses is weak [3–6]. Furthermore, whilst much is known about the contribution of HIV to adult mortality,

remarkably little is known about the mortality attributable to HIV during the pregnancy and postpartum period.

Two approaches have been used to estimate the proportion of maternal deaths attributable to HIV. First, a systematic review of the causes of maternal deaths in population-based studies, published in 2006, suggested that 6.2% of maternal deaths in Africa had been attributed to HIV/AIDS [7]. This estimate was based on only eight studies, and verbal autopsies used to assign the causes of death did not define the criteria for classifying a maternal death as HIV/AIDS-related.

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Due to the lack of empirical data, mathematical models are the second main source of estimates of the proportion of maternal deaths attributable to HIV. Two models have gained credence, each yielding very different estimates of the proportion of maternal deaths due to HIV for 2008, the most recent year where both models provide estimates. In a model developed by the Institute for Health Metrics and Evaluation (IHME) [8], 17.9% of maternal deaths worldwide were attributed to HIV. In contrast, the Maternal Mortality Estimation Inter-agency Group (MMEIG) estimated that only 5.9% of maternal deaths were due to HIV/AIDS globally [2]. The two models differ in a number of ways, including the predictor variables used in the regression models, but the main difference probably lies in the assumptions made about the number of deaths to HIV-infected pregnant and postpartum women which should be attributed to pregnancy and therefore classified as maternal. In the IHME model, all deaths occurring amongst HIV-infected pregnant and postpartum woman are classified as maternal deaths while the MMEIG assumes that only half of the deaths occurring in HIV-infected pregnant and postpartum woman should be classified as maternal deaths.

We propose an alternative method to estimate the proportion of pregnancy-related deaths due to HIV. In this paper we report data on the risk ratio (RR) and the prevalence of HIV from a systematic review of studies that compare mortality during pregnancy and the postpartum in HIV-infected and uninfected women. We calculate summary estimates of the relative and attributable risks for the association between HIV and mortality during pregnancy and the postpartum period. To assess the impact of the HIV epidemic on pregnancy related mortality at the population level, we calculate population attributable fractions for each study individually and under scenarios of varying HIV prevalence using the pooled RR obtained from the meta-analysis.

Methods

Search strategy

A review protocol outlining the methods for our systematic review was developed and reviewed by external experts. We searched bibliographical databases (PubMed, EMBASE, Popline) and a WHO regional database (African Index Medicus (AIM)) on July 6, 2011. A single comprehensive search strategy for each database was developed using MeSH and free-text words. For the bibliographical databases, articles were included if their abstract, title or keywords contained a pregnancy/postpartum term, an HIV/AIDS term and a term related to mortality, obstetric complications or HIV progression. For the simpler AIM database, a reduced search was conducted, including all studies referring to both

pregnancy/postpartum and HIV/AIDS. The search strategy is available in Supplementary File S1. Additional publications were identified by manually searching the reference lists of included articles. There were no language restrictions.

Inclusion and exclusion criteria

Titles and abstracts identified by the search strategy were screened by a single reviewer (CC) and full texts were sought for relevant articles. A 20% sample of the titles and abstracts was screened by a second reviewer to cross-check the identification of articles by the first reviewer.

Studies were eligible for inclusion if they compared mortality during pregnancy, delivery and/or up to 365 days postpartum between HIV-infected and uninfected women using a cohort, census or case-control study design. Mortality could either be defined as "pregnancy-related" (including all deaths) or "maternal" (excluding deaths which were accidental or incidental to the pregnancy) [9]. Any studies assigning the HIV status of women through clinical assessment rather than using HIV testing were excluded. Studies were required to have a sample size of at least 30 women in each study group with no restrictions on study country, dates or whether the study was population or facility based. Conference abstracts were excluded.

Data extraction

Data for each study were extracted by a single author (CC) on: location of study, study dates, study design, study population, definition of pregnancy-related or maternal death, gestational age at recruitment and length of postpartum follow-up, HIV prevalence in the study population, whether antiretroviral therapy (ART) was available, the number of deaths by HIV status, the type of denominator (live births/ women/ women-years) and the denominator.

For any study where data were available for multiple definitions of maternal or pregnancy-related mortality, that closest to the ICD-10 definition of a pregnancy-related death was used [9]. Where data on the prevalence of HIV or ART availability amongst pregnant women were not available from the published paper, estimates were obtained from UNAIDS for the same time period and region or country. Data duplicated in different papers were only extracted once.

Assessment of the risk of bias

- (1) The risk of bias for each study was assessed according to the following criteria:
- (2) Loss to follow-up: Inadequate if loss to follow-up was greater than 20% or more than 20% of the deaths had unknown HIV status or no information was provided on loss to follow-up
- (3) Adjustment for confounders: Inadequate if there was no adjustment for confounders or if there was no attempt to

- match HIV-infected and uninfected women on potential confounders
- (4) Definition of pregnancy-related death: Inadequate if the time period in which women were observed was not stated or unclear
 - (5) Ascertainment of pregnancy-related death: Inadequate if the study design used was likely to lead to pregnancy-related deaths being missed (e.g. record review in facilities)
 - (6) Selection of comparison group: Inadequate if HIV-uninfected women were unlikely to be representative of the population from which the HIV-infected women were selected (e.g. if HIV-uninfected women were selected from different hospitals or antenatal clinics than HIV-infected women)

Data analysis

The pregnancy-related mortality risk in HIV-infected and uninfected women was defined as the number of pregnancy-related deaths per 100,000 pregnant women. In studies only reporting live births the risk was expressed per 100,000 live births. For each study, the risk ratio (RR), attributable risk (AR) and population attributable fraction (PAF) were calculated [10].

A meta-analysis was conducted using Stata 12.0 to calculate both the pooled RR and pooled AR quantifying the increased risk of a pregnancy-related death in HIV-infected women compared with uninfected women. Given the variation in study design the DerSimonian-Laird random effects method was used to combine study estimates [11]. Stratified analyses were conducted to explore the effects of geographical region (as a proxy for the stage of HIV epidemic), availability of ART, whether the study was population-based and the length of the postpartum follow-up on the pooled RR for the association between HIV and pregnancy-related mortality. Meta-analyses were conducted for each quality criterion outlined previously, stratifying the pooled RR by whether they were judged to be of adequate quality or not.

In order to assess the impact of the HIV epidemic on pregnancy-related mortality at the population level, the PAF was calculated under scenarios of varying HIV prevalence using the overall pooled RR obtained from the meta-analysis according to the following formula:

$$PAF = \frac{p(RR - 1)}{(p(RR - 1)) + 1}$$

Where:

- *p* is the prevalence of HIV
- RR is the pooled risk ratio

Results

Fig. 1 quantifies the number of studies excluded at each stage of the review process. 18,949 potentially relevant articles were identified, of which 17,640 were excluded through abstract and title screening. From the 1,291 full texts obtained (18 full texts were unavailable), 23 studies contained data on the risk of pregnancy-related mortality in HIV-infected and uninfected women.

A description of the 23 eligible studies is contained in Supplementary Table S1. Study populations were from South Africa [12–14], Tanzania [15], Republic of Congo [16], Democratic Republic of Congo [17], Malawi [18], Zimbabwe [19–21], Rwanda [5,22], Uganda [23–25], Kenya [26], India [27,28], Spain [29], the USA [30,31] and Mexico [32]. One study included women from two different countries (Malawi and Zambia) [33]. The majority of studies followed women throughout pregnancy and up to either 42 days or one year postpartum. One study followed women throughout pregnancy until the end of delivery [32] and three studies did not follow women during pregnancy: women were followed from delivery to 15 days postpartum [22]; from active labour to one year postpartum [17] and from within 96 hours of delivery to one year postpartum [21]. The remaining eight studies did not provide sufficient information on the timing during pregnancy and the postpartum period. Two studies were population-based [16,25], with all others recruiting women from hospitals or antenatal clinics. Two of these studies recruited women who were at high risk of mortality: one was conducted in a high risk obstetric unit [13] while the other recruited women who were admitted to hospital in pregnancy during seasonal outbreaks of malaria [20]. Two studies only included women having caesarean sections [29,31].

In 22 studies the pregnancy-related mortality risk was higher in HIV-infected women than uninfected women, varying from 3.7 to 21.6 times higher. One study conducted in Rwanda found that HIV-infected women had a lower risk of death compared with uninfected women (RR: 0.33, 95% CI 0.01–8.17) [22]. This study was small, only picking up one pregnancy-related death. Meta-analysis of the RR from the 23 studies indicated that HIV-infected women had eight times the risk of a pregnancy-related death compared with uninfected women (pooled RR: 7.74, 95% CI 5.37–11.16) (Fig. 2). There was strong evidence for between-study heterogeneity ($I^2 = 54.1\%$, $P = 0.001$).

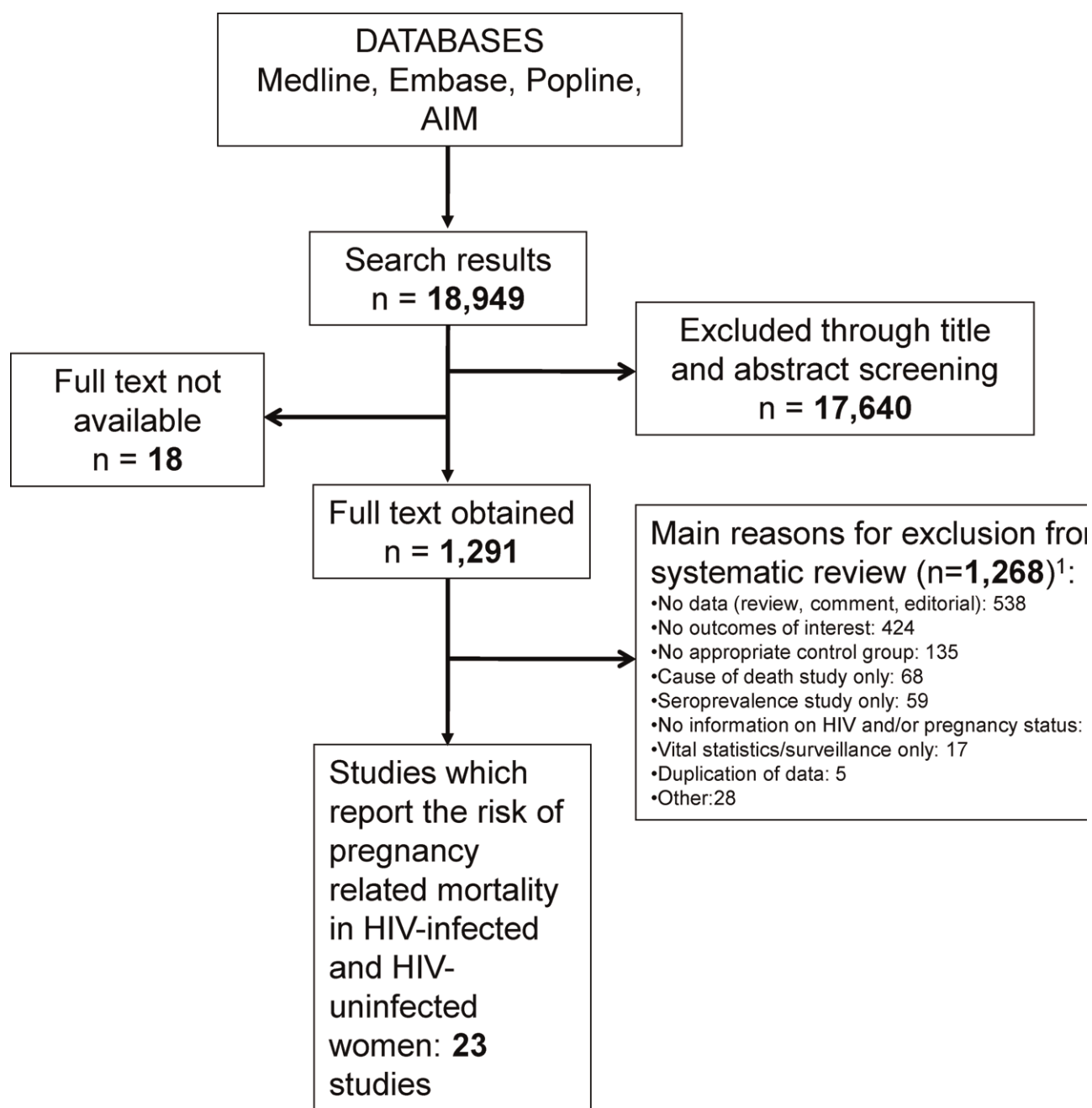


Fig. 1. Flow chart of study selection for inclusion in the systematic review¹ Articles may have been excluded for multiple reasons.

The results of the stratified meta-analyses are presented in Table 1. No clear patterns emerged. In East Africa, where the majority of the studies were conducted, the RR was 7.21 (4.36–11.92). Higher RRs were found in the USA and South Asia, but there were only two studies in each of these regions. The pooled RR was higher for the five studies conducted when ART was available compared with studies conducted when it was not available (10.65 vs. 6.86), but the confidence intervals overlapped. The two population-based studies had a smaller pooled RR

than the 20 facility based studies (4.42 (95% CI: 2.23–8.38) and 8.70 (95% CI: 5.99–12.62) respectively).

Studies using a definition which included the period beyond 42 days postpartum had more than double the pooled RR (11.47, 95% CI 7.99–16.48) compared with those which only pertained to the pregnancy, delivery or up to 42 days postpartum (4.78, 95% CI 3.23–7.06) (Table 1). Studies which did not provide a clear definition of the follow-up period also had a high pooled RR of 11.68 (95% CI 7.19–18.97). Whilst there was still weak

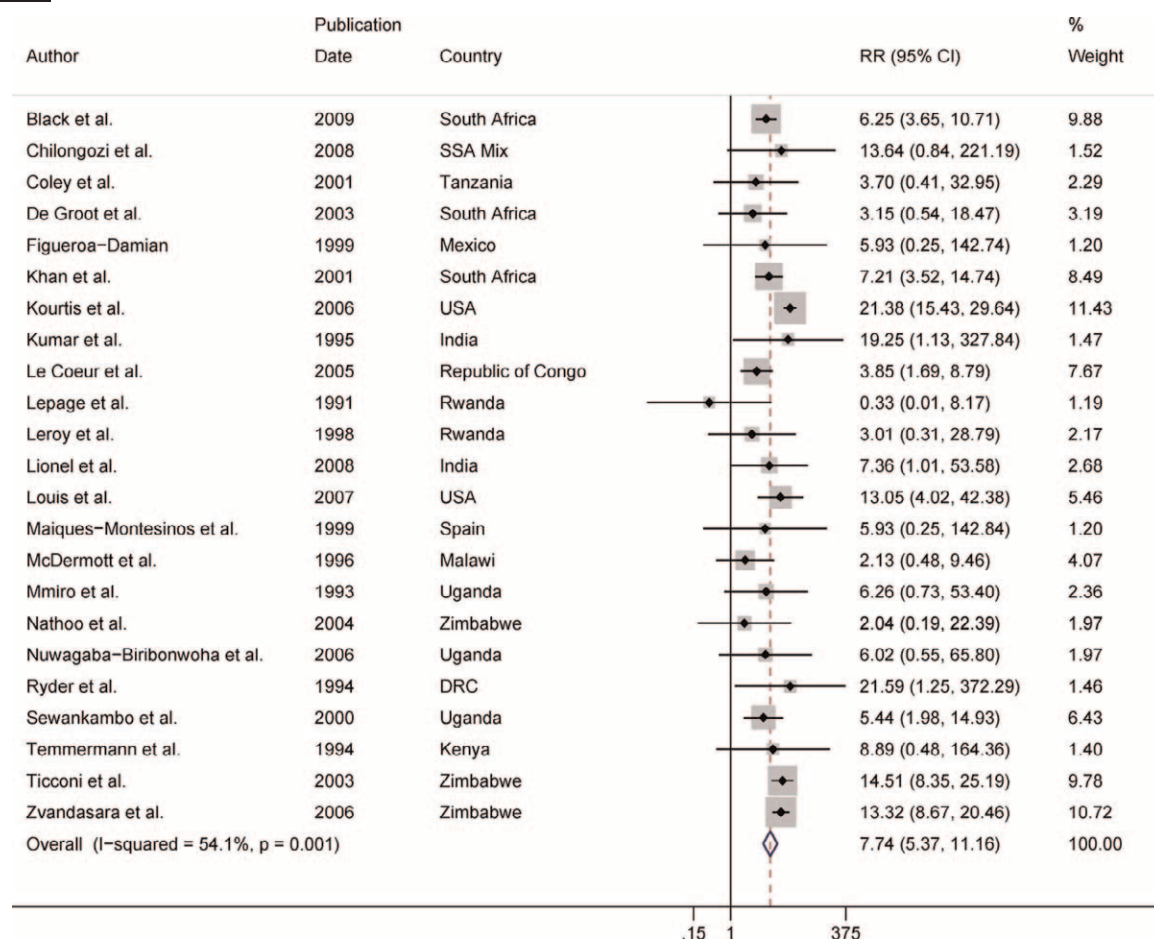


Fig. 2. Forest plot showing the strength of association between HIV and pregnancy-related mortality.

Table 1. Meta-analysis of the risk ratio for pregnancy-related mortality in HIV-infected women compared with uninfected women stratified by region, whether the study was population or facility based, ART availability and the length of the postpartum period included.

	Number of studies	Pooled risk ratio (95% CI)	I ²	p-value
Region				
South Africa	3	6.31 (4.16–9.59)	0	0.70
East Africa	12	7.21 (4.36–11.92)	36.4	0.10
Middle Africa	2	5.21 (1.44–18.78)	23.0	0.25
South Asia	2	10.10 (1.99–51.34)	0	0.59
North America	2	20.64 (15.07–28.28)	0	0.43
Central America	1	5.93 (0.25–142.74)	–	–
South Europe	1	5.93 (0.25–142.84)	–	–
Study population				
Population based	2	4.42 (2.34–8.38)	0	0.60
Facility based	21	8.70 (5.99–12.62)	48.3	0.007
ART Availability				
Not available	17	6.86 (4.60–10.23)	34.3	0.08
Available	6	10.65 (5.11–22.21)	68.9	0.007
Period of follow-up				
Pregnancy, delivery and/or up to 42 days postpartum	11	4.78 (3.23–7.06)	0	0.74
Extend postpartum period at risk beyond 42 days	5	11.47 (7.99–16.48)	0	0.52
Unclear	8	11.68 (7.19–18.97)	44.4	0.08

Table 2. Meta-analysis of the risk ratio for pregnancy-related mortality in HIV-infected women compared with uninfected women stratified by quality of studies for each quality criterion.

Quality Criterion	Studies of adequate quality		Studies of inadequate quality	
	N	Pooled risk ratio (95% CI)	N	Pooled risk ratio (95% CI)
Loss to follow-up	10	5.43 (2.89–10.21)	13	9.42 (5.94–14.92)
Adjustment for confounders	7	4.55 (1.62–12.82)	16	8.26 (5.62–12.15)
Ascertainment of pregnancy-related death	15	7.05 (4.34–11.46)	8	8.53 (4.69–15.50)
Definition of a pregnancy-related death	15	6.31 (4.14–9.62)	8	11.68 (7.19–18.97)
Selection of comparison groups	20	7.75 (5.27–11.40)	3	6.05 (1.33–27.47)

evidence for between-study heterogeneity amongst studies which did not have a clear follow-up period ($I^2 = 44.4\%$, $p = 0.08$), for the other two groups there was no evidence for between-study heterogeneity ($I^2 = 0\%$).

The quality assessment for each study is presented in Supplementary Table S2. Overall, most of the studies were judged to be of inadequate quality for at least one of the quality criteria. The pooled RR, stratified by whether the study was judged to be of adequate quality for each quality criterion are presented in Table 2. There is little difference between the pooled estimates from adequate and inadequate studies for each methodological issue with the exceptions of the pregnancy-related death definition and adjustment of confounders. For these criteria, the pooled RR was nearly double for studies judged to have inadequate quality compared with those of adequate quality, but differences were not statistically significant.

The excess risk of pregnancy-related mortality attributable to HIV amongst women who were HIV-infected (AR) ranged from 174 per 100,000 pregnant women in South Africa [14] up to 28386 per 100,000 pregnant women in Zimbabwe [20] (Supplementary Table S1). Overall, the pooled AR from all the studies was 994 per 100,000 women (95% CI: 677–1310). There was very high heterogeneity between the studies ($I^2 = 89.4\%$, $P < 0.001$).

Based on the prevalence of HIV determined either from the study or from UNAIDS estimates, the PAF for individual studies ranged from 0.7% in Spain [29] to 78.7% in a study from Zimbabwe [21] (Supplementary Table S1, Figure 3). Individual PAFs exceeded 40% in studies from South Africa [12,14], Zimbabwe [20,21], Rwanda [5], Uganda [23,25], the Democratic Republic of Congo [17] and Kenya [26]. Using the summary RR of 7.73, we calculated the PAF for varying prevalences of HIV (Fig. 3). For a region where the HIV prevalence is 2% amongst pregnant and postpartum women, it is predicted that 11.9% of all deaths during pregnancy and the period up to one year postpartum are attributable to HIV/AIDS. This figure rises to 50.2%, if the prevalence of HIV increases to 15%.

Discussion

In this review we find that a very high proportion of pregnancy-related deaths are attributable to HIV at the population level. The substantial excess mortality attributable to HIV among HIV-infected pregnant and postpartum women (pooled AR 994 per 100,000 pregnant women) has a major impact on all-cause pregnancy-related mortality in the population, even where the prevalence of HIV is relatively low. In areas where the HIV prevalence among pregnant women is as low as 2%, 12% of all pregnancy-related deaths may be attributable to HIV. This figure rises to 50% in areas with an HIV prevalence of 15% among pregnant women. UNAIDS estimates that the prevalence of HIV in adults of reproductive age in 2011 was 0.8% globally and 4.9% in sub-Saharan Africa [34]. Based on these prevalence figures we estimate that approximately 5% of pregnancy-related deaths worldwide and 25% in sub-Saharan Africa are attributable to HIV.

The excess mortality attributable to HIV in HIV-infected pregnant and postpartum women is not surprising. In the absence of ART, which was the case for most of the studies reviewed here, a substantial number of HIV-infected women will have progressed to clinical stages of HIV/AIDS, with high mortality as a result. The magnitude of the excess is higher than expected however. Women who are in the late stages of HIV disease are less likely to become pregnant [35], and pregnant HIV-infected women are thought to be healthier than non-pregnant HIV-infected women [16,36]. In two population-based studies the excess mortality attributable to HIV was much smaller in pregnant than in non-pregnant HIV-infected women [16,25]. Non-pregnant HIV-infected women were 40 times more likely to die than HIV-uninfected women in the Congo and 26 times more likely in Uganda. This can be compared to the equivalent figures of four and five times respectively in pregnant and postpartum women. Most of the studies included here were facility-based, possibly selecting for a population of pregnant women who are at higher risk of death. However, for this to result in an upward bias in the relative and attributable risks in relation to HIV the selection of high risk women would have had to be stronger in the HIV-infected than in the HIV-uninfected.

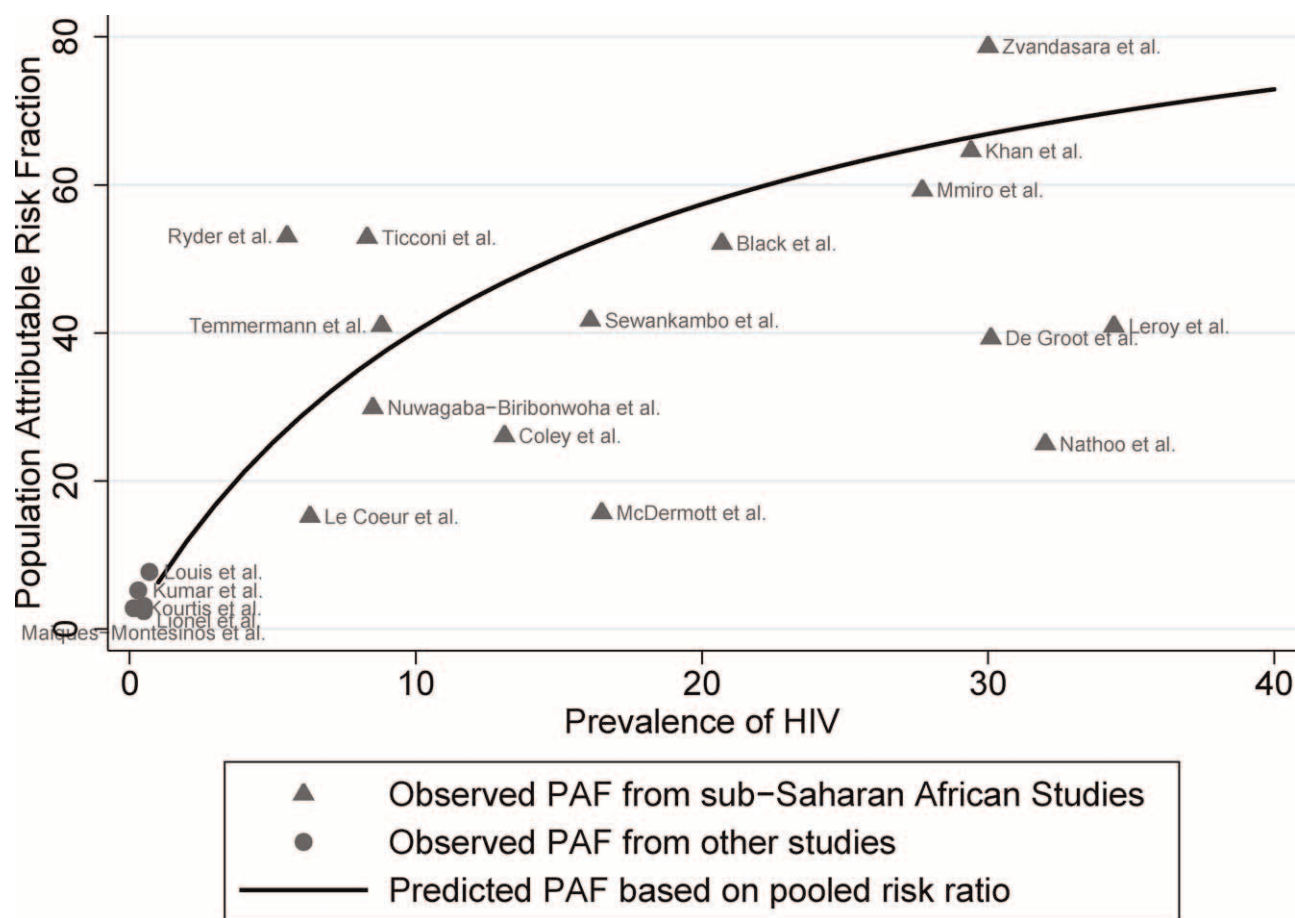


Fig. 3. The population attributable fraction for the proportion of deaths attributable to HIV amongst pregnant/postpartum women. Individual data points show the observed PAF for each study and the curve shows the PAF predicted using the pooled risk ratio from all the studies.

Our approach to estimating the impact of HIV on pregnancy-related mortality has two main advantages compared to previous studies. First, we use empirical rather than modelled data on the relationship between HIV and pregnancy-related mortality. Our summary estimate of an eight-fold relative risk of pregnancy-related mortality comparing HIV-infected and uninfected pregnant and postpartum women is based on data from 23 studies across the world. This result does need to be interpreted with some caution as there was strong evidence for between-study heterogeneity in the RR. Consequently the summary estimate obtained should be interpreted as an average RR about which the true study RRs actually vary. Previous estimates of the proportion of maternal deaths that are attributable to HIV, on the other hand, have made various assumptions about the relationship between HIV and pregnancy-related mortality. The IHME model estimates the proportion of maternal deaths attributable to HIV by calculating the difference in the predicted number of maternal deaths comparing mathematical models including and excluding HIV prevalence. They thus assume that all deaths in HIV

infected women are attributable to HIV [8,37]. The MMEIG model uses a more complex model based on two key assumptions about (1) the proportion of AIDS deaths among all women of reproductive that occur to pregnant women and (2) the proportion of pregnancy-related deaths to HIV-infected women that qualify as maternal deaths [2,38]. Since there are no empirical data supporting any of the assumptions the validity of either of the models is impossible to verify.

Second, by estimating the contribution of HIV to pregnancy-related rather than maternal mortality no assumptions need to be made about whether HIV is indirectly related or coincidental to the pregnancy. The distinction between indirect and coincidental mortality requires knowledge on whether a death in an HIV-infected women may have been accelerated by the pregnancy, an event which is nearly impossible to ascertain. Very few studies examining the causes of maternal death specify how HIV-related indirect deaths can be distinguished from HIV-related coincidental deaths. A recent WHO document suggests that deaths in HIV-infected pregnant and postpartum women should

be categorised into direct obstetric deaths, “AIDS related indirect maternal deaths” (who die because of the aggravating effect of pregnancy on HIV) and “HIV-related deaths” (who die of a fatal complication of HIV or AIDS that is coincidental to the pregnancy) [39]. However, no guidance is given as to how this distinction should be made. Given that most pregnancy-related deaths in HIV-infected women occur in sub-Saharan Africa where cause of death information relies on verbal autopsies, the prospect of being able to distinguish AIDS-related indirect deaths from HIV-related coincidental deaths is limited [40]. Conditions such as severe anaemia and tuberculosis, for example, can be treated as causes of both indirect maternal deaths and HIV-related deaths, and it is not clear how such deaths should be classified. Reporting pregnancy-related rather than maternal mortality would overcome these problems, and research efforts should focus on identifying deaths “with” rather than “from” HIV.

Our review was comprehensive in nature and it is unlikely that relevant studies have been missed. However, the relatively small number of retained studies restricted our ability to conduct stratified analyses, sometimes allowing larger studies to drive the summary estimates. For example, the pooled RR for studies which stretched the postpartum period at risk of dying beyond 42 days is dominated by a single study from Zimbabwe, which recruited women just after delivery and excluded any women with acute life-threatening conditions [21]. Each study was classified for stratification by covariates which may not have reflected the characteristics of the whole study population. This is particularly pertinent when interpreting the results related to ART availability since we had no data on the proportion of individuals on ART. No studies adjusted any of the RR for confounders; although several studies did match the HIV-infected and uninfected women on age and parity, and one study also matched the women on socio-economic status. Consequently the PAFs we estimate for varying prevalences of HIV, which are mostly based on crude RR may have been over-estimated.

One of the main strategies to reduce HIV-related mortality is to widen access to ART treatment. In this review, there was no evidence for a difference in the pooled RR for studies conducted when ART was available compared to those where ART was not available; however this result needs to be interpreted with caution. Only two of the studies with ART available were conducted in sub-Saharan Africa and the studies were predominantly undertaken when ART was only initiated if CD4 cell counts were very low. If all HIV-infected women were on ART we would expect to see a lower ratio in the pregnancy-related mortality risk comparing HIV-infected and uninfected women.

The impact of the HIV epidemic on pregnancy-related mortality is substantial, with more than half such deaths attributable to HIV in high prevalence settings. This has implications for integrated service delivery as well as for monitoring trends in MDG5 – maternal mortality. Safe motherhood programmes should extend their remit beyond the prevention of direct obstetric causes of death, and integrate HIV services into their programmes in order to reduce the levels of pregnancy-related mortality. Furthermore, the monitoring of pregnancy-related rather than maternal mortality avoids making assumptions about whether an HIV-related death is indirectly related or coincidental to the pregnancy, allowing for more reliable monitoring of levels and causes particularly where estimates rely on verbal autopsy data. Future research should focus on how to identify HIV-related deaths using verbal autopsies, so that pregnancy-related mortality can be monitored including and excluding HIV-related deaths.

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CC and CR designed the study and prepared the manuscript. CC screened the articles, extracted the data and conducted the analysis.

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Conflicts of interest

None Declared.

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