The Contribution of HIV to Mortality in Pregnant and Postpartum Women

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STATEMENT OF OWN WORK

I, Clara Ann Durie Calvert, confirm the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: …….. Date: ……

ABSTRACT

Background: High levels of HIV and maternal mortality go hand in hand in many regions of sub-Saharan Africa. Therefore, understanding the interaction between pregnancy and HIV is important, not only for the clinical management of pregnant women, but also for the measurement of maternal mortality, the standard definition of which excludes infectious causes of death not aggravated by pregnancy.

Methods: In this thesis the excess mortality attributable to HIV in pregnant and postpartum women is calculated by comparing the risk of mortality in HIV-infected pregnant and postpartum women to their uninfected counterparts using two different data sources: 1) studies identified through a systematic review and; 2) data from six demographic surveillance sites (DSS) in sub-Saharan Africa. Verbal autopsy (VA) data from the DSS are also used to explore the percentage of deaths classified as HIV/AIDS-related. Two additional systematic reviews are conducted to assess whether HIV increases the risk of obstetric complications, or pregnancy accelerates HIV disease progression.

Results: HIV-infected women have eight times the risk of pregnancy-related mortality compared with HIV-uninfected women. Based on this estimate, we predict that roughly a quarter of deaths in pregnant or postpartum women are attributable to HIV in sub-Saharan Africa. A lower percentage of pregnancy-related deaths are attributed to HIV/AIDS using VA data. There is little evidence that HIV-infected women are at increased risk of direct obstetric complications, with the exception of sepsis, or that pregnancy increases the risk of HIV disease progression.

Conclusion: HIV may cause up to 25% of deaths during pregnancy and in the postpartum period in areas of high HIV prevalence. Most of the evidence suggests that this excess pregnancy-related mortality attributable to HIV is largely coincidental to pregnancy. This implies that there is little reason to discourage healthy, HIV-infected women from becoming pregnant if they desire to do so.

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ACRONYMS AND ABBREVIATIONS

ARTI	Acute Respiratory Tract Infection
AIDS	Acquired Immune Deficiency Syndrome
AIM	African Index Medicus
ALPHA	Analysing Population-based HIV/AIDS data on Africa
ANC	Antenatal Care
AR%	Attributable Risk Percentage
ART	Antiretroviral Therapy
CI	Confidence Interval
CoD	Cause of Death
CSMF	Cause-specific Mortality Fraction
DSS	Demographic Surveillance Site
GDP	Gross Domestic Product
HAART	Highly Active Antiretroviral Therapy
HR	Hazard Ratio
HIV	Human Immunodeficiency Virus
ICD-10	10th Revision of the International Classification of Disease
IHME	Institute of Health Metrics and Evaluation
LSHTM	London School of Hygiene and Tropical Medicine
MDG5	Millennium Development Goal 5
MeSH	Medical Subject Headings
MMEIG	Maternal Mortality Estimation Interagency Group
MMR	Maternal Mortality Ratio
MOOSE	Meta-analysis of Observational Studies in Epidemiology
OR	Odds Ratio
PAF	Population Attributable Fraction
PPP	Pregnant or postpartum
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses

PY	Person-years
RaR	Rate Ratio
RiR	Risk Ratio
RR	Relative Risk
TB	Tuberculosis
UNAIDS	The Joint United Nations Programme on HIV/AIDS
VA	Verbal Autopsy
VCT	Voluntary Counselling and Testing
WHO	World Health Organization

1 BACKGROUND

1.1 INTRODUCTION

In many parts of sub-Saharan Africa, women of reproductive age face relatively high risks of dying both from HIV and from complications associated with pregnancy. In 2010, there were an estimated 1,490,000 pregnant women living with HIV, 91.2% of whom were in sub-Saharan Africa,(1) while estimates of HIV prevalence amongst women attending antenatal clinics were as high as 30.2% in South Africa,(2) 16.1% in Zimbabwe,(3) and 10.6% in Malawi.(4) Given the substantial HIV burden in pregnant women in sub-Saharan Africa, the public health importance of understanding the possible interaction between HIV and pregnancy has been raised by a number of researchers.(5, 6) Unfortunately, methodological and conceptual issues have made quantifying the contribution of HIV to maternal mortality challenging.

This thesis uses epidemiological data to assess the impact of HIV on mortality in pregnant and postpartum women, and to explore possible biological interactions between HIV and pregnancy. In this chapter, a brief overview of the literature will be provided, summarising the conceptual difficulties in measuring maternal mortality, what is already known on the contribution of HIV to mortality in pregnancy and the postpartum and on the interaction between HIV and pregnancy, as well as highlighting the knowledge gaps which have driven this PhD research. At the end of this chapter the objectives and structure of this thesis will be outlined.

1.2 INTERSECTING EPIDEMICS: MATERNAL MORTALITY AND HIV

1.2.1 Measuring the burden of maternal mortality

Millennium Development Goal 5 (MDG5) was set in 2000 with the target of reducing the maternal mortality ratio (MMR) by 75% between 1990 and 2015. Progress towards this target has been made with recent estimates indicating that maternal mortality is decreasing worldwide;(7) however, in some regions the number of deaths from pregnancy-related complications remains unacceptably high. In sub-Saharan Africa, for example, it has been estimated that 510 maternal deaths occurred for every 100,000 live births in 2013, more than 30 times higher than the MMR for developed regions.(7) The reasons for the high MMRs in parts of sub-Saharan Africa are likely to be complex, including issues such as poor health system infrastructure. HIV/AIDS is also thought to be one of the main drivers of high MMRs,(8-10) with researchers noting, for example, that the MMR increased by a factor of 2.5 between 1985-1994 and 1995-1999 in Zimbabwe when the HIV/AIDS epidemic was growing.(10) However, empirical evidence supporting the role of HIV in maternal mortality is weak, primarily due to the scarcity of data, but there are additional difficulties introduced by the definition of maternal death.

In the 10th revision of the International Classification of Diseases (ICD-10), a maternal death is defined as “the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes”.(11) This definition encompasses both direct obstetric deaths, when the death occurred as a result of an obstetric complication such as haemorrhage or eclampsia, and indirect obstetric deaths, when either an underlying medical condition or disease which developed during pregnancy is aggravated by the pregnancy. Deaths thought to be incidental to pregnancy are excluded from maternal mortality estimates, but are included as pregnancy-related deaths which are defined in ICD-10 as any “death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death”.(11)

In practice, disentangling causes of deaths which are aggravated by pregnancy is challenging, leading to varied criteria for defining indirect obstetric deaths. For example, in the “Mother’s mortality and severe morbidity” study all communicable diseases except chickenpox, gonorrhoea, herpes and hepatitis C were considered non-maternal causes of death,(12) whereas in the 1994-1996 UK confidential enquires into

maternal deaths, all communicable diseases, with the exception of Creutzfeldt-Jakob disease, were classified as maternal causes of death.(13) Similarly, some studies suggest that certain causes of death which are often excluded from maternal mortality estimates, such as suicide and violence, may be attributable in some way to the pregnancy.(14, 15)

Classifying HIV/AIDS-related deaths as maternal deaths has also proved controversial, with uncertainty surrounding whether and when HIV should be considered as an indirect or incidental cause. Figure 1.1 illustrates how HIV/AIDS-related deaths which occur during pregnancy and in the postpartum should be classified according to ICD-10. Theoretically, HIV/AIDS-related deaths should only be counted as indirect maternal deaths if pregnancy accelerated HIV disease progression or if pregnancy increased the risk of acquiring HIV, although no guidance has been provided on how to ascertain when HIV was aggravated by pregnancy.(16) Such uncertainty has led to differing assumptions on the percentage of HIV/AIDS-related deaths which should be classified as maternal.

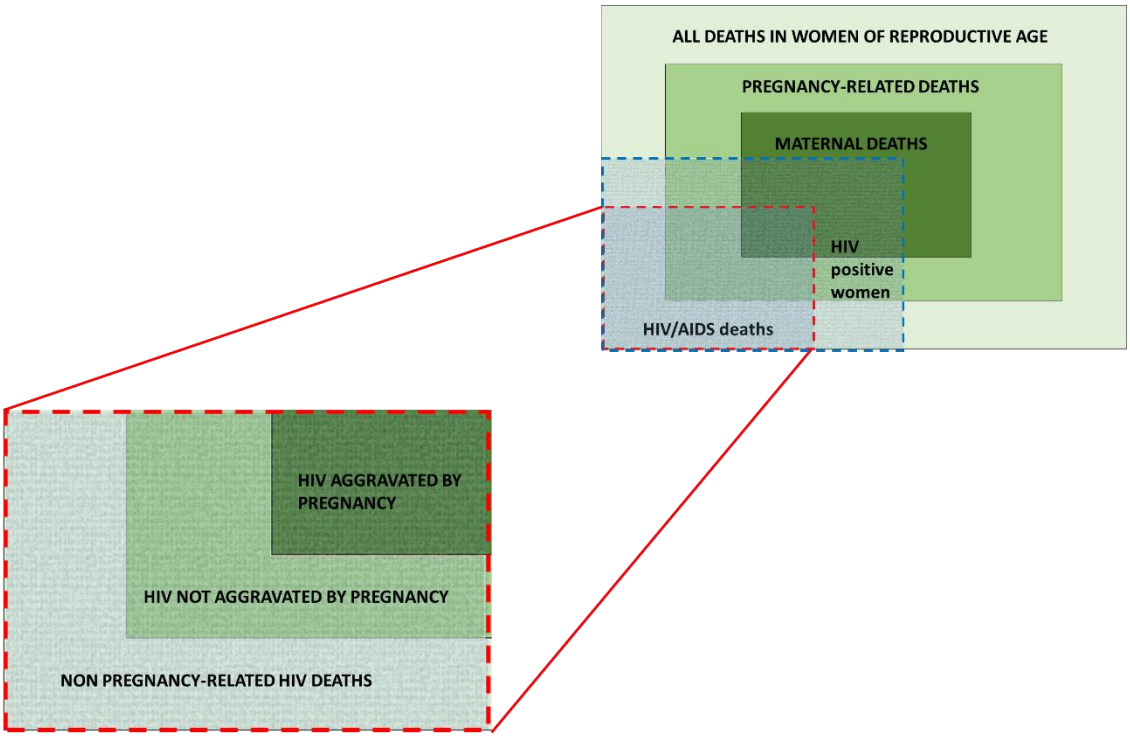

Figure 1.1: Classifying HIV/AIDS deaths in women of reproductive age (adapted from Rosen et al., 2012 (17))

1.2.2 Estimating the contribution of HIV to maternal mortality

Data on the contribution of HIV to maternal mortality in sub-Saharan Africa come from two main sources: local-level epidemiological studies and global-level mathematical models.

Epidemiological Studies

In areas with high HIV prevalence, some facility-based studies have found HIV/AIDS to be one of the leading causes of maternal deaths.(18-21) In a tertiary hospital in South Africa, for example, over 40% of maternal deaths were attributed to HIV/AIDS,(20) while in a study conducted across nine facilities in Central Malawi 16% of maternal deaths were assigned as HIV/AIDS-related.(18) Such studies indicate that HIV is likely to have a substantial impact on levels of maternal mortality; however, the extent to which these facility-based studies represent causes of maternal deaths at the population level is questionable given the low levels of institutional delivery across many parts of sub-Saharan Africa.

Population-based data on the causes of maternal deaths in sub-Saharan Africa are scarce, with few deaths in the region captured by vital registration systems.(22) Consequently, studies ascertaining causes of maternal deaths predominately rely on verbal autopsy (VA). VA is an interview where family members and/or caregivers of the deceased are asked about the signs and symptoms occurring before the death.(23, 24) Symptom data from VA interviews are usually interpreted by physicians, although automated methods are increasingly being used to assign the cause of death.(23) Many studies have assessed the validity of these methods for identifying HIV/AIDS-related deaths amongst adults;(25, 26) however, to our knowledge, the validity of VA interpretation methods for assigning HIV/AIDS amongst deaths to women who were pregnant or postpartum have not been explored, and there has been no attempt to assess whether it is possible to disentangle which HIV/AIDS-related deaths may have been aggravated by pregnancy.

A systematic review of population-based cause of death studies published between 2003 and 2013 identified 19 studies which reported the percentage of pregnancy-related or maternal deaths attributable to HIV/AIDS in sub-Saharan Africa.(27) Based on a meta-analysis of these studies, 3.4% of pregnancy-related deaths in sub-Saharan Africa were estimated to be attributable to HIV/AIDS, but with regional variation: from 1.1% in West Africa up to 26.1% in Southern Africa. The authors of the study conclude, however, that the overall quality of the studies was poor and the summary estimates

should be interpreted with caution: 15 of the 19 studies relied on VA; only 13 of the studies attributed any deaths to HIV/AIDS and provided very few details, if any, on the criteria for assigning deaths as HIV/AIDS-related; and 11 of these 13 studies considered HIV as an indirect cause of maternal death without providing any rationale for this classification.

Mathematical Models

The scarcity of empirical data on the contribution of HIV to maternal mortality means most estimates of the impact of HIV on maternal mortality rely on mathematical models that make assumptions about the extent to which HIV interacts with pregnancy; yet the exact nature of this relationship is poorly understood due to the lack of empirical data. There are two main mathematical models which have been developed, one by the Institute for Health Metrics and Evaluation (IHME) and the other by the Maternal Mortality Estimation Inter-agency Group (MMEIG).

In the IHME model (published in 2010) several covariates, selected based on published work and existing theories, were used to predict maternal mortality at the national and global level.(28) These covariates were total fertility rate, gross domestic product (GDP) per capita, HIV seroprevalence, age-specific female education, neonatal mortality and age. Through this regression model it was estimated that there were 342,900 (uncertainty interval: 302,100-394,300) maternal deaths worldwide in 2008. The percentage of these deaths that were due to HIV was estimated by setting HIV seroprevalence to zero in the model, and observing the difference in the predicted global number of maternal deaths. Under this scenario it was calculated that the number of maternal deaths in 2008 would have been reduced to 281,500, suggesting that HIV contributed to 17.9% of maternal deaths. This percentage rises to 31.9% in sub-Saharan Africa.(17) Underlying these estimates is the assumption that all deaths occurring amongst HIV-infected pregnant woman should be classified as maternal. A similar methodology was adopted for an IHME model published in 2011.(29) As with the 2010 model, all HIV/AIDS deaths were counted as maternal; however, the number of HIV/AIDS-related deaths were calculated using information on the number of HIV/AIDS-related deaths by age for women, and multiplying this by the time spent pregnant. Worldwide, 20.5% of maternal deaths were attributed to HIV/AIDS; unfortunately it was not possible to work out the corresponding percentage for sub-Saharan Africa based on the published article. The most recent model from IHME (30) incorporates work presented in this thesis and, as such, is discussed in the final chapter of this thesis.

The MMEIG also sought to predict maternal mortality levels for 2008 using modelling techniques, and estimated that the worldwide number of maternal deaths was 358,000 [95% confidence interval (CI): 265,000-503,000].(31) The treatment of HIV in this model differed considerably from the IHME model. In the first part of the modelling procedure, HIV/AIDS-related deaths were removed from the data. This was done by calculating the proportion of HIV/AIDS-related deaths in women that occur during the pregnancy or postpartum period using data on the general fertility rate, the average women years lived in the maternal risk period per live birth, and the relative risk from dying from AIDS for a pregnant versus non-pregnant women. Then, using non-AIDS related maternal deaths as the outcome, a similar regression model to the IHME model was developed, with the following covariates: general fertility rate, GDP per capita and skilled birth attendance. Finally, a fraction of the HIV/AIDS-related deaths among pregnant women that qualify as maternal because of some causal relationship with pregnancy were re-included in the estimates from the model to provide the final results.

Unlike in the IHME model, the MMEIG model assumes that only half of the HIV/AIDS-related deaths occurring in pregnant woman should be classified as maternal deaths and thus re-introduced into the final estimates. Correspondingly, this model produces lower estimations for the effect of HIV/AIDS, with 5.9% of maternal deaths due to HIV/AIDS globally, and 9.0% in sub-Saharan Africa. The model developed by the MMEIG was updated to estimate the number of maternal deaths for 2010.(32) Using very similar methodology to the 2008 model, it was estimated that there were 287,000 maternal deaths in 2010 (95% CI: 230,000-398,000), of which 6.5% worldwide and 10.4% in sub-Saharan Africa were attributed to HIV/AIDS. The 2014 model from MMEIG also incorporates results from this PhD, and will be presented in the final discussion of this thesis.(7)

Comparison of Estimates

From the current data, both modelled and empirical, it appears that the HIV epidemic has impacted on levels of maternal mortality. There is, however, substantial variation in the percentage of maternal deaths attributed to HIV/AIDS (Figure 1.2), and these data do not provide evidence either that HIV increases the risk of direct or indirect causes of death, or that pregnancy aggravates HIV.

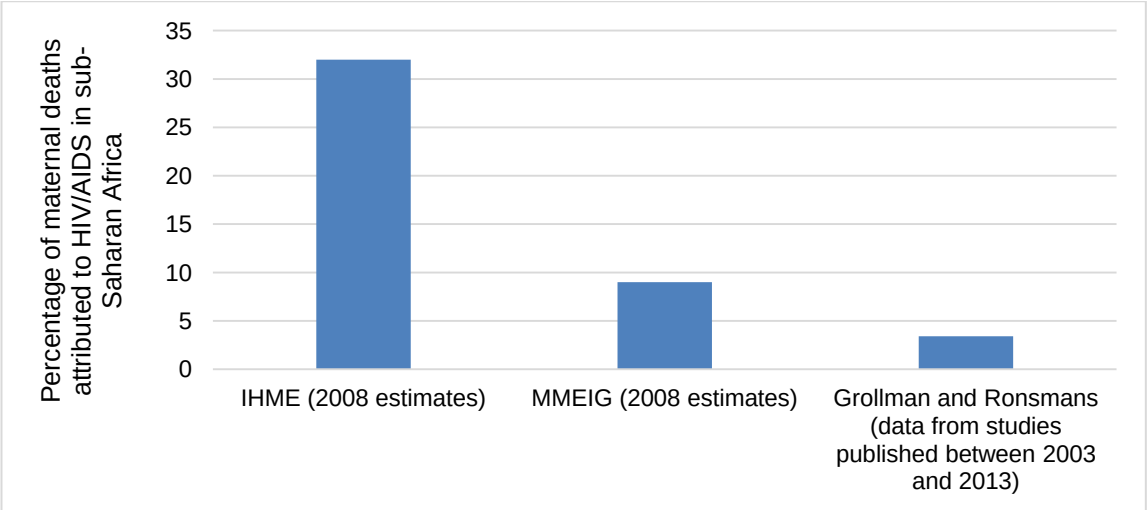

Figure 1.2: Comparison of estimates of the percentage of maternal deaths attributable to HIV/AIDS in sub-Saharan Africa

1.2.3 Interaction between HIV and pregnancy

There are a number of different mechanisms through which HIV and pregnancy may interact to increase the risk of death during the pregnancy or postpartum period. Pregnancy may accelerate HIV disease progression or increase HIV incidence, or pregnant women with HIV may be at greater risk of obstetric complications or death from other indirect causes of maternal death. It is also plausible, however, that HIV-infected pregnant women may die from HIV/AIDS regardless of the pregnancy.

The effect of pregnancy on HIV disease progression

It was hypothesised at an early stage of the HIV epidemic that pregnancy may accelerate HIV disease progression as immune adaptations are known to occur during pregnancy and HIV leads to immune suppression.(33) One of the main immunological impacts of HIV is the depletion of CD4 T cells.(34, 35) These cells form a key component of cell-mediated immunity signalling the presence of an infectious particle to other immune cells, for example CD8 T cells and B cells that can destroy the infected cells.(36)

Pregnancy has also been hypothesised to alter cell-mediated immunity based on the observed reduction in CD4 T cells, CD8 T cells and B cells with advancing pregnancy.(37, 38) This hypothesis has been supported by a study in mice,(39) and through widely documented improvements in cell-meditated autoimmune disorders, such as multiple sclerosis and rheumatoid arthritis during pregnancy.(40, 41) Clinical and epidemiological evidence has supported an association between pregnancy and increased severity of several infectious diseases including influenza,(42, 43) hepatitis

E,(44) and the herpes simplex virus.(45) However, it is unclear whether the immune suppression associated with HIV is exacerbated in pregnant women.

Some studies of HIV-infected women found that CD4 T cell counts decrease faster during pregnancy,(46, 47) although one of these studies found that CD4 T cell counts rebound in the postpartum period.(46) Others studies have not found any effect of pregnancy on immunological markers in HIV-infected women.(48-50) A systematic review published in 1998 did not find evidence that pregnancy accelerates HIV disease progression, but did find some weak evidence that the odds of death or acquiring an AIDS-defining illness are higher amongst HIV-infected pregnant than HIV-infected non-pregnant women.(51) However, seven out of the eight studies included in this review were from high income countries with the remaining study conducted in Haiti.(52) The Haitian study did find that disease progression was more likely in pregnant than non-pregnant women, leading some authors to suggest that the effect of pregnancy on disease progression may be stronger in resource-poor settings.(5) New studies from low-income countries have been published since this meta-analysis, though it has not been updated.

The effect of pregnancy on HIV incidence

During pregnancy, physiological changes (e.g. increased ectopy) and changes in a woman's or her partner's sexual behaviour may lead to increased susceptibility to HIV.(53) A recent systematic review identified two studies which compared the risk of HIV acquisition in pregnant/postpartum women to that in non-pregnant women.(54) Based on a meta-analysis of these studies, there was no evidence that pregnancy increased the risk of HIV acquisition (pooled hazard ratio=1.2, 95% CI: 0.7-1.8). Since this systematic review, a study has been published using data from six community-based HIV cohorts which form part of the ALPHA network.(55) In this study, pregnancy was associated with a lower risk of HIV acquisition after adjusting for site and age (hazard ratio=0.79, 95% CI: 0.70-0.89).

The effect of HIV on direct and indirect causes of maternal mortality

Both biological and social factors may lead to an increased risk of direct obstetric complications with HIV infection. Several plausible biological pathways have been hypothesised. The immunosuppressive effects of HIV may put women at risk of infections, including puerperal sepsis.(6) Additionally, HIV-related thrombocytopenia, where there is a low platelet count in the blood, may increase a woman's risk of haemorrhage.(56) Poor access to healthcare including antenatal care (ANC) and skilled birth attendance at delivery, may be exacerbated in HIV-infected women due to

social factors, such as the discrimination and stigma these women face in some settings.(57, 58) A study in Kenya, for example, found that some HIV-infected women were reluctant to deliver in a facility for fear of their HIV status being disclosed to family members.(58)

There has not been a systematic effort to synthesise all the existing knowledge about whether HIV-infected women are at greater risk of direct obstetric complications, despite dozens of studies investigating HIV as a risk factor for obstetric complications including haemorrhage, eclampsia and infection. Epidemiological evidence for an increased occurrence of postpartum haemorrhage amongst HIV-infected compared to HIV-uninfected women was found in a study conducted in Rwanda(59) but not in studies conducted in the USA(60) and France.(61) Conflicting results have also been found in studies looking at the effect of HIV on the risk of pre-eclampsia and eclampsia.(62-64) Finally, studies of major complications following caesarean sections, for example sepsis, have found a higher risk in HIV-infected women compared with HIV-uninfected women in developed countries.(65, 66) However, a more recent study conducted in Uganda did not find such an association.(67)

It is also plausible that HIV increases the risk of maternal mortality by increasing susceptibility to, and severity of, indirect causes of maternal death such as tuberculosis (TB), malaria and anaemia. A number of studies have linked HIV infection during pregnancy with increased risk of acquiring malaria.(68-71) In Kenya, for example, malaria acquisition was 1.7 times more likely amongst HIV-infected pregnant women compared with HIV-uninfected pregnant women (95% CI: 1.52–1.90).(68) This study also found that HIV-infected pregnant women with malaria had higher malaria parasite densities than HIV-uninfected women with malaria. HIV infection has also been identified as a risk factor for anaemia during pregnancy,(72) and this effect may be particularly severe when the pregnancy is also complicated by malaria.(73, 74)

1.2.4 Impact of ART on association between HIV and pregnancy

The impact of HIV on mortality in pregnant and postpartum women is likely to have been influenced by antiretroviral therapy (ART), access to which was very low in sub-Saharan Africa until 2003.(75) Numerous studies have shown significantly lower HIV/AIDS-related mortality rates amongst HIV-infected individuals on ART. In KwaZulu-Natal, South Africa, for example, HIV/AIDS-related mortality rates amongst adults 15-49 years old dropped from 114.3 per 10,000 person-years in 2000 to 58.3 per 10,000 person-years in 2009.(76) Similarly, in Karonga, Malawi, the AIDS-related mortality rate

reduced from 50.5 per 10,000 person-years to 16.0 per 10,000 person-years following the introduction of ART.(77)

Several studies have demonstrated a mortality reduction in pregnant and postpartum women with ART. Buchmann *et al.* linked the introduction of ART to a decline in the MMR in a maternity hospital in Johannesburg, South Africa.(21) In Dar es Salaam, Tanzania, it was found that women enrolled in an HIV/AIDS treatment program who were on ART at delivery had a 34% lower risk of mortality compared to women not on ART.(78) An even stronger protective effect was observed amongst women who were on ART before the pregnancy [odds ratio (OR): 0.45, 95% CI: 0.29-0.70], with a strong linear relationship observed between increasing time on ART during pregnancy and reduction in pregnancy-related mortality (8% lower risk of mortality with each extra month of ART in pregnancy).(78) Similarly, using data from Malawi and Mozambique, it was found that mortality among women who received less than a month of highly active antiretroviral therapy (HAART) prior to delivery was triple that of women who received HAART for more than three months prior to delivery.(79)

Any biological interaction between HIV and pregnancy may have also been modified with the availability of ART. A review published in 2009,(80) concluded that pregnancy may have a protective effect on HIV disease progression with HAART availability; however this conclusion was based on a single study.(81) The effect of ART on the association between HIV and obstetric complications may vary depending on the type of obstetric complication. For some obstetric complications, any detrimental impact of HIV may be attenuated due to the improved health of the HIV-infected woman with ART. However, ART has been linked with increased risks of pre-eclampsia and gestational diabetes mellitus,(82) and while the general consensus is that the benefits of ART outweigh the potential risk during pregnancy(82, 83) the importance of continuing to monitor the possible adverse effects in pregnancy is widely acknowledged.

1.3 OVERALL AIMS AND OBJECTIVES

Quantifying the percentage of deaths to pregnant and postpartum women attributable to HIV/AIDS is important for determining the priority interventions of Safe Motherhood programmes and for assessing the impact of interventions to reduce these deaths. Information on whether there is an interaction between HIV and pregnancy which increases a woman's mortality risk is also important for two main reasons. First, it helps inform fertility choices for HIV-infected women who wish to have a child (i.e. how safe

is pregnancy?). Second, it improves our understanding of the contribution of HIV to maternal mortality, in particular which deaths in HIV-infected pregnant women should be counted as maternal.

Despite the importance of understanding the impact of HIV on mortality during the pregnancy period, there are still substantial knowledge gaps. Notably, estimates of the contribution of HIV to maternal mortality have had to make assumptions of the percentage of HIV/AIDS-related deaths which were aggravated by pregnancy, and have generally relied on the interpretation of VA data, the validity of which is unclear in pregnant and postpartum women. Furthermore, the mechanisms underlying any excess mortality attributable to HIV in pregnant and postpartum women are not well understood. There has been no attempt to synthesise the evidence on whether HIV increases the risk of direct obstetric complications, and while reviews have attempted to synthesise the evidence on the association between pregnancy and HIV disease progression, studies from sub-Saharan Africa were not identified and the effect of ART on any association remains unclear.

Therefore, the overall aim of this thesis is to estimate the contribution of HIV to mortality during pregnancy and the postpartum period using empirical data, and to examine the possible mechanisms which may explain any excess HIV-attributable mortality in pregnancy.

Specific objectives are as follows:

Objective 1: To calculate the excess mortality attributable to HIV in pregnant and postpartum women, and examine whether this varies with ART availability

Objective 2: To ascertain whether HIV increases the risk of direct obstetric complications

Objective 3: To assess whether pregnancy accelerates HIV disease progression, and whether any association between pregnancy and HIV disease progression is modified by the availability of ART

Objective 4: To assess the validity of using VA data to identify HIV/AIDS-related deaths amongst all women of reproductive age, and to explore whether this varies by pregnancy status

1.4 STRUCTURE OF THIS THESIS

An overview of the data sources and methodologies used to address the aims and objectives of the thesis are presented in Chapter 2.

The majority of the results sections of this thesis (Chapters 3-6) follow the research paper style, with research articles incorporated into broader chapters. The text of the articles has not been edited, although in some cases material which was originally presented in appendices has been moved to the body of the research article and the bibliography of the articles have been combined with that from the rest of this thesis (Chapter 9). The final results chapter (Chapter 7) has not yet been prepared for publication and, consequently, is formatted in a more traditional thesis style chapter.

Chapters 3-5 present results from systematic reviews. Chapter 3 presents the results of a systematic review of studies which quantify the increased risk of mortality in HIV-infected pregnant and postpartum women compared with their uninfected counterparts, and the percentage of pregnancy-related mortality attributable to HIV is predicted for varying prevalences of HIV using the pooled relative risk from these studies (Objective 1). The second review, reported in Chapter 4, provides an overview of the literature reporting on the association between HIV and direct obstetric complications (Objective 2). The final systematic review paper brings together studies which look at the effect of pregnancy on HIV disease progression (Objective 3).

The remaining two results chapters are based on secondary analyses of data from community-based studies from Eastern and Southern Africa. Chapter 6 aims to quantify the excess mortality attributable to HIV in pregnant and postpartum women (Objective 1) through a secondary analysis of data from six of the sites. In Chapter 7, the validity of two different methods of identifying HIV/AIDS-related deaths from verbal autopsy (VA) data are explored (Objective 4).

Finally, Chapter 8 brings together the results from each of the preceding chapters, and provides an overview of the implications of the study findings for public health and for the measurement of maternal mortality.

2 METHODS

Two main data sources were used to address the study objectives. Firstly, three systematic reviews were conducted, each addressing one of the following objectives:

Review 1: To calculate the excess mortality attributable to HIV in pregnant and postpartum women

Review 2: To ascertain whether HIV increases the risk of direct obstetric complications

Review 3: To assess whether pregnancy accelerates HIV disease progression

Subsequently, data from six community-based, longitudinal sites in Eastern and Southern Africa were used to calculate the excess mortality attributable to HIV in pregnant and postpartum women and to assess the validity of using verbal autopsy (VA) data to identify HIV/AIDS-related deaths.

As the methods are only briefly summarised in each article, this chapter aims to provide a broader and more detailed overview of the methods used across the thesis. It is divided into three sections. The first section describes the methods used to conduct the systematic reviews, while the second provides detailed descriptions of the data available for the sites in Eastern and Southern Africa and how this was prepared for analysis. In the final section, the role of the candidate is outlined.

2.1 SYSTEMATIC REVIEW

A systematic review protocol was initially developed outlining the aim of each review, the inclusion criteria, and setting out the types of analyses which would be conducted (Appendix A, page 234). The protocol was reviewed by several researchers with expertise in maternal health and systematic reviews. All the systematic review papers were prepared using either the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (84) or the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines,(85) both of which were developed to improve the reporting of systematic reviews.

2.1.1 Search strategy

Potentially relevant articles for the systematic review were identified by searching bibliographical databases (Medline, EMBASE, Popline) and a World Health Organization (WHO) regional database [African Index Medicus (AIM)]. A single comprehensive search strategy for each database was developed using Medical Subject Headings (MeSH) and free-text words with the aim of capturing literature for all three systematic reviews. 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 relating to any one of the above three objectives. For the simpler AIM database, a reduced search was conducted, including all studies referring to both pregnancy/postpartum and HIV/AIDS. The full search strategy is provided in Appendix B (on page 243).

2.1.2 Study selection and inclusion criteria

All titles and abstracts identified by the search strategy were screened by the candidate and full texts were sought for all potentially relevant articles. A 20% sample of the titles and abstracts was selected systematically (50 abstracts per 500 abstracts, organised in alphabetical order according to the authors name) and were screened by a second reviewer (Christopher Grollman) to cross-check the identification of articles. All articles which were identified as potentially relevant by the second reviewer but not by the first reviewer were investigated: none of these met the inclusion criteria.

Appropriate study groups, outcomes, and study designs for inclusion are summarised for each review in Table 2.1. There were no restrictions on study country, dates or whether the study was population or facility-based.

Table 2.1: Type of studies required for each review

	Review 1 (excess mortality)	Review 2 (obstetric complications)	Review 3 (HIV disease progression)
Exposed Group	HIV+ women who were pregnant and/or up to one year postpartum	HIV+ women who were pregnant and/or up to one year postpartum	HIV+ pregnant women (regardless of the definition of the length of the pregnancy or postpartum period at risk)
Comparison Group	HIV- women who were pregnant and/or up to one year postpartum	HIV- women who were pregnant and/or up to one year postpartum	HIV+ non-pregnant women
Outcomes	Mortality ("pregnancy-related" or "maternal") during pregnancy, delivery and/or up to one year postpartum	• Obstetric haemorrhage • Intrauterine infections • Pregnancy-induced hypertension • Dystocia	• AIDS-related Mortality • An AIDS-defining illness • Drop of CD4 count • A condition indicative of symptomatic HIV • All-cause mortality
Suitable Study Designs	• Cohort • Case control • Cross sectional	• Cohort • Case control • Cross sectional	• Cohort • Case control
Additional inclusion criteria	• HIV status had to be ascertained using HIV testing rather than clinical criteria • At least 30 women in each study group		NONE

Due to the limited information available in conference abstracts, these were not included.

2.1.3 Data extraction and data quality

A data extraction form was prepared in Microsoft Excel for each review, and data were extracted from each relevant study by the candidate. Across all reviews data were extracted on:

- Study setting
- Study design
- Study population
- ART availability
- Definition and method of measuring the outcome
- Measure of effect (crude and adjusted)

For each review a set of quality criteria were selected; these are outlined in detail in the individual systematic review chapters (Chapter 3 – Chapter 5). In line with recommendations from the Cochrane Collaboration, we did not attempt to produce an overall quality score for each study because scoring systems are difficult to validate and often reflect whether information was reported, rather than how the study was conducted.(86) We instead used a "domain-based evaluation" where the risk of bias for

each of the quality criteria was assessed and presented separately across all the studies.(86)

2.1.4 Data analysis

Data for all reviews were entered and analysed in STATA. The DerSimonian–Laird random effects model was used to produce pooled estimates for all three reviews. A random effects model was used as most studies relied on observational data, and there was variation between the study populations and methods.(87) Under the random-effects meta-analysis model all pooled effect estimates should be interpreted as an average of the individual study effect estimates which are genuinely different from one another.(88)

2.2 ALPHA NETWORK DATA ANALYSIS

For the second part of this thesis, I used secondary data from the Analysing Population-based HIV/AIDS data on Africa (ALPHA) network (http://alpha.lshtm.ac.uk/) which brings together ten community-based, longitudinal studies in sub-Saharan Africa, all of which collect information on the HIV status of the population. This data enabled us to build on the findings from the first systematic review paper – which aimed to quantify the excess pregnancy-related mortality associated with HIV – using population-based data from sub-Saharan Africa. All of the sites collect verbal autopsy (VA) data and so I also explored how this VA data may be used to identify HIV/AIDS-related deaths, and whether these methods are valid in pregnant and postpartum women. This section will cover the methods from the point of data collection up to and including the data preparation for analysis; details of the statistical analyses are provided in Chapter 6 and Chapter 7.

2.2.1 The study areas

All sites in ALPHA are cohorts which monitor whole communities. They cannot, however, be considered nationally representative with marked differences often observed between the ALPHA communities and national level statistics. There are currently ten sites which make up the ALPHA network; however, four of the sites did not have sufficient HIV data when the analyses were being conducted for this PhD, and are therefore not included.

The six sites which contributed data for the PhD are: Karonga in Malawi; Kisesa in Tanzania; Manicaland in Zimbabwe; uMkhanyakude in South Africa; and Masaka and Rakai, both of which are in Uganda (Figure 2.1).

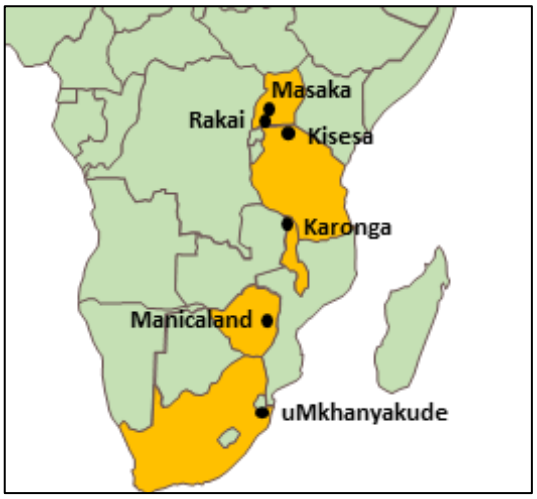

Figure 2.1: Location of the ALPHA sites

These sites have all completed several rounds of demographic surveys and HIV testing and conducted VAs. Basic information about each site is contained in Table 2.2.

Table 2.2: Characteristics of ALPHA study sites contributing data on HIV and pregnancy-related mortality

Study Site	Population size (2008)	Demographic surveillance		HIV serosurvey		Verbal Autopsy data collection periods
		Start date	Frequency of data collection	Start date	Frequency of data collection	
Karonga	33,500	2002	Continuous	2007[1]	1 year	2002-present
Kisesa	28,000	1994	6 months	1994	3 years	1994-present
Manicaland	30,000	1998	2-3 years	1998	2-3 years	1999-2006
Masaka	7,000	1989	Annually	1989	Annual until 2011 then biannual	1990-1992 & 2006-2008
Rakai	14,000	1994	14-16 months	1994	14-16 months	1996-present
uMkhanyakude	86,000	2000	6 months	2003	1 year	2000-present

[1]**Some earlier data available from small-scale studies**

2.2.2 Data collection methods

Whilst each site collects similar data, there are differences between the sites in the start date, frequency of data collection and in the exact information which is obtained. The methods of data collection at each site are described in detail below.

Karonga

In Karonga, the demographic surveillance site (DSS) data have been continuously collected using key informants, who are trained to record vital events and movements within their cluster of households.(89) HIV surveillance is conducted based on voluntary counselling and testing (VCT) and began in September 2007,(77) although

some earlier data are available from small-scale studies which were conducted in the community. VA data are collected by a medically trained interviewer as soon as possible after a death is reported, after allowing a two week mourning period.(77, 90)

Kisesa

DSS data are collected every six months, and HIV data collected approximately every three years in Kisesa.(91, 92) HIV testing is conducted for research purposes without results disclosure; however, since 2000, participants have had access to a free health clinic which provides VCT.(92) VA data are collected through interviews conducted by a clinical officer with the caregiver of the deceased. These data were collected from the start of the DSS, initially using its own VA questionnaire (1994-2002) followed by the INDEPTH tool, before finally switching to an adapted version of the WHO-recommended standard VA in 2007.

Manicaland

Manicaland was set up to explore the dynamics of the HIV epidemic, and consequently, it does not conduct frequent rounds of household enumeration. Demographic data are collected retrospectively at serosurveys which occur approximately every 2-3 years. HIV testing is conducted only for research purposes.(93) VA data are collected through interviews conducted by medical officers or nurses with the deceased's primary caregiver if a death is identified during a serosurvey. The VA questionnaire is a modified version of that used in Kisesa between 1994 and 2002.(94)

Masaka

In Masaka, demographic and HIV surveillance started in 1989. DSS data are collected through an annual household census, and through key informants who register births and deaths on a monthly basis. HIV testing was undertaken annually until 2011, with biennial surveys conducted subsequently. HIV test results are reported back to respondents if requested. VA data were only collected in Masaka in 1990-1992 and again in 2006-2008 using a VA tool developed at the site. The VA data were collected from relatives of the deceased by a nurse approximately two months after the death.(25)

Rakai

In Rakai, DSS and HIV data are collected at 14-16 month intervals. Cohort participants are encouraged to receive their HIV results through community based counsellors. If a death is recorded during the DSS interview then a VA questionnaire, which was

developed in Rakai, is used to collect information on the signs and symptoms of the deceased during the same interview.

uMkhanyakude

DSS data are collected every six months, and the HIV serosurveys are conducted every year in uMkhanyakude.(95, 96) Participants can obtain their HIV test results from counselling centres in the research area.(96) There is a high refusal rate for HIV testing.(96) A VA is conducted for all deaths reported in the DSS by a trained nurse and, on average, occur six months following the death.(76)

Data for identifying pregnant and postpartum women: comparison of sites

Of key importance to this PhD work are the methods the sites use to identify pregnancies and births. The type of DSS data collected from each site on births and pregnancies and the frequency of data collection is summarised in Table 2.3. Data on gestational age are not collected.

Table 2.3: Type of birth data available at each study site

Study Site	Frequency of DSS data collection	Data collected on births	Data collected on stillbirths	Data collected on pregnancy reports
Karonga	Continuous	✓	✓	×
Kisesa	Every 6 months	✓	×	✓
Manicaland	Every 2-3 years	✓	×	✓
Masaka	Annually	✓	×	✓
Rakai	Every 14-16 months	✓	✓	×
Umkhanyakude	Every 6 months	✓	✓	✓

2.2.3 Data sources

Data analysts from each site prepared standardised data sets for ALPHA, five of which were used for this PhD. Data specifications were provided to ensure that the data from each site could be pooled to produce one consistent data set (Appendix C, page 250). As part of this PhD work, I helped with the preparation of the specification for the VA data; all the other specifications were put together by other members of the ALPHA study team. In brief, the data sets contain the following information:

1. **DSS residence episodes**: entry and exit date, entry type (baseline, birth or in-migration) and exit type (still present in study site, death, out-migration, loss to follow up) for calculating person-years of observation and dates of death

2. **HIV test data**: dates and results of HIV tests for the classification of individuals by HIV status and tracking of any changes in this status over time
3. **Birth records**: date of birth and, if available, information on stillbirth
4. **Pregnancy interview records**: date of pregnancy report where available
5. **VA data**: information on the signs and symptoms preceding a death from proxy respondents for assigning cause of death

2.2.4 Data management and preparation

Data cleaning and pooling

On receipt of the data sets from the sites, basic checks were conducted to ensure that all the necessary variables were present and coded correctly. Basic analyses were then undertaken to check that the data provided sensible estimates of, for example, HIV prevalence and fertility rates. Inconsistencies which were noted by the candidate were relayed to the sites in the form of a data report.

The data sets for the analyses presented in Chapter 6 were pooled by the candidate on the 12th February 2013. Updated versions of many of the data sets were available when the VA analysis for Chapter 7 was conducted; therefore the data were re-pooled on the 9th July 2014. Once the data were pooled there were three main time-varying variables which needed to be produced before analyses could be undertaken: pregnancy status, HIV status and ART availability. The methods used to produce these variables are described below.

Assigning pregnancy status

Birth and pregnancy reports were merged with the residency information to assign women of reproductive age time spent pregnant or postpartum (PPP) or not PPP. For several reasons it is likely that women who die are more likely to be incorrectly classified as non-pregnant when only DSS data is used. Firstly, pregnancies which do not result in a live birth may be missed as a birth date may not be recorded. Secondly, if a woman dies after delivering a baby, the baby may be moved out of the household and consequently the birth may not be recorded for the woman who died. In light of such limitations the VA data were used to identify additional pregnancies and deliveries occurring in women who were recorded as dying in the DSS. For these cases, the date of birth was assumed to be one week before the date of death where the deceased was reported to have recently delivered a baby. Where a death during pregnancy was reported, the pregnancy report was set to be three days before the date of death.

Different assumptions were made to assign person-time spent pregnant or postpartum, depending on whether there was a birth or pregnancy report. Where a birth was reported (in the DSS or VA data), the woman was classified as PPP for the 280 days preceding and the 42 days after the birth. An interval from 43-365 days postpartum and from 1-2 years postpartum was also assigned. If a stillbirth was reported, then the allocated pregnancy time was reduced from 280 days to 180 days.

Where a reported pregnancy was matched to a birth report, only the birth report was retained. However, pregnancy reports without a matching birth report were more problematic as it was not possible to know during which stage of the pregnancy it was reported. It was assumed that women were unlikely to report a pregnancy in the first 90 days, therefore delivery dates were calculated as follows:

1. Where there was only one pregnancy report, it was assumed to occur halfway between the 90th day of pregnancy and the end of pregnancy.
2. Where there were two pregnancy reports for a single pregnancy the interval between the two reports was calculated. If this interval was less than 190 days then the midpoint of the interval was assumed to be at the centre of the 90-280 day window where pregnancies would be expected to be reported. When the interval was greater than 190 days, the first pregnancy report must have occurred during the first 90 days of pregnancy. Therefore, the midpoint of the interval between the two pregnancy reports was assumed to fall in the middle of the full length of a pregnancy (280 days).

After calculating a delivery date for the unmatched pregnancy reports, the type of birth (stillbirth or live birth) was assigned based on whether the woman was still under observation in the study at the time of their estimated delivery date. Women who left the study site before their estimated delivery date and did not return to the study until afterwards were treated as if they had a live birth. Pregnancy reports where the estimated delivery date occurred when the woman was still in the study site were treated as stillbirths, as it would be expected that a live birth would be reported in the DSS. In these cases, pregnancy time was adjusted to give a shorter gestational period.

Some simple graphical examples of how person-time spent pregnant/postpartum is allocated based on delivery or pregnancy reports are provided in Figure 2.2.

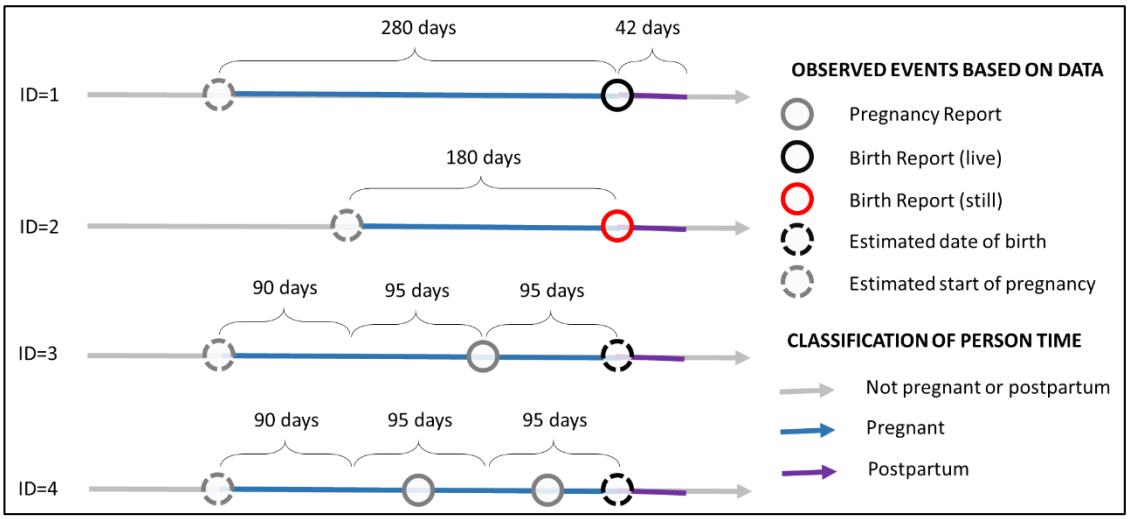

Figure 2.2: Classification of person-time as pregnant/postpartum or not pregnant or postpartum based on pregnancy and delivery reports (from either DSS data or verbal autopsy)

Assigning HIV status

Person-time needed to be further broken down into time spent as HIV-infected and HIV-uninfected. HIV test information was therefore merged with the residency data file containing information on pregnancy status. Figure 2.3 shows how person-time would be assigned as HIV-infected, HIV-uninfected and HIV status unknown based on observed test results, for six different study participants. Individuals with a negative HIV test result date but no positive HIV result date were assumed to remain HIV negative for a period equivalent to the time it would be expected for approximately 5% of the cohort to seroconvert (1.5 years in uMkhanyakude, three years in Manicaland and five years in the other sites) and thereafter were classified as HIV status unknown. Those with a first positive HIV test result date but no record of an HIV negative test were assumed to be HIV positive from the time of the first test result. Individuals who had dates for both a last negative HIV test result and a first positive HIV result were assigned a seroconversion date as the midpoint between these two dates. Finally, all person-time of those who did not have an HIV test was classified as HIV status unknown.

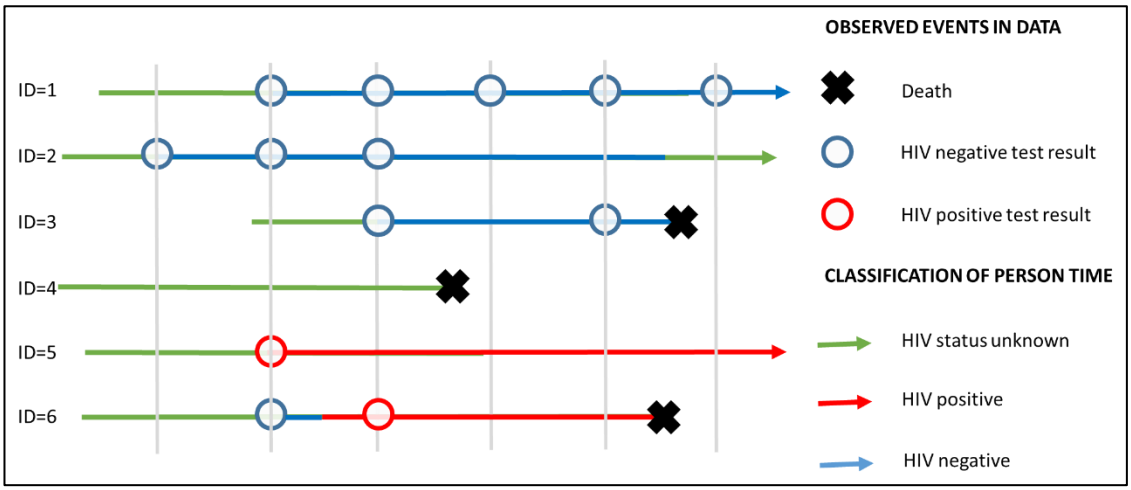

Figure 2.3: Classification of person-time as HIV status unknown, HIV-infected and HIV-uninfected based on HIV test results

A family member/caregiver may report a women who had not tested positive in a serosurvey as HIV-infected in a VA; therefore, to avoid counting these deaths without allocation of an appropriate amount of person-time at risk, we assumed that women who were established to be HIV-infected on the basis of VAs had been infected for half the median post-infection survival time in the pooled data set which equates to approximately five years.(97)

Assigning phases of ART availability

Individual level data on ART use were not available. Therefore, information on the dates of introduction of ART in each study area were obtained from researchers at each of the sites, and were used to classify three time periods: before the introduction of ART; a roll-out phase of ART during which time ART is assumed to only be partially available; and, finally, a phase which captures the time from when ART became widely available in the study site. The start dates for the "ART roll-out" phase and the "ART widely available" phase are shown in Table 2.4.

Table 2.4: Dates for the introduction of ART, and the full roll-out of ART

	Start of data collection	ART roll-out	ART fully available
Karonga	2002	July 2005	October 2006
Kisesa	1994	March 2005	September 2008
Manicaland	1998	January 2007	January 2009
Masaka	1989	January 2004	January 2005
Rakai	1994	January 2004	June 2006
uMkhanyakude	2000	January 2004	January 2006

2.2.5 Ethical considerations

Ethical approval for all secondary analyses undertaken as part of this PhD was granted by the London School of Hygiene and Tropical Medicine (LSHTM) ethics committee (ref: 6522).

2.3 ROLE OF THE CANDIDATE

The candidate decided on the research objectives for the systematic reviews, wrote the systematic review protocol, conducted the database search, undertook the title and abstract screening, located and screened full-texts, extracted data from relevant articles, analysed the data and wrote up the findings. At all stages input was sought from supervisors.

In the analysis of the ALPHA data, the candidate did not play any role in collecting primary data or translating the data from the site databases to a standard format according to the ALPHA data specifications. The candidate worked alongside other members of the ALPHA network to pool, clean and prepare the data (i.e. create the pregnancy status variable) for analysis. The candidate designed the analysis plan, undertook all analyses and wrote up the findings.

For all the papers, the candidate wrote the initial draft and incorporated comments from co-authors. This process was shared with Basia Zaba for the paper presented in Chapter 6.

3 THE CONTRIBUTION OF HIV TO PREGNANCY-RELATED MORTALITY: A SYSTEMATIC REVIEW AND META-ANALYSIS

3.1 INTRODUCTION

This chapter presents the results from a systematic review which aimed to quantify the percentage of excess mortality attributable to HIV amongst pregnant and postpartum women, and thereby address the first objective of this thesis. This work was published in AIDS as an open access article in June 2013 (see (98) for the published version of the article).

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   I am the first author on this paper. I was responsible for the research design, undertaking the systematic review and conducting the meta-analysis. I was also primarily responsible for writing this work. My co-author supported this work in an advisory capacity and by helping to edit the writing.

NAME IN FULL (Block Capitals) CLARA CALVERT

STUDENT ID NO: 236162

CANDIDATE'S SIGNATURE ……..…….
Date

SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above)

……..……

3.2 ARTICLE

3.2.1 Abstract

Objectives: Although 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 article 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 HIV-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: Twenty-three studies were included (17 from sub-Saharan Africa). Meta-analysis of the risk ratios indicated that HIV-infected women had eight times the risk of a pregnancy-related death compared with HIV-uninfected women [pooled risk ratio: 7.74, 95% confidence interval (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.

3.2.2 Introduction

Among women of reproductive age, HIV/AIDS is the leading cause of death (99) and women in sub-Saharan Africa also experience the highest levels of maternal mortality. (31) 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.(51, 59, 60, 100) Furthermore, although 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.(101) 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.

Owing 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 in which both models provide estimates. In a model developed by the Institute for Health Metrics and Evaluation (IHME),(28) 17.9% of maternal deaths worldwide were attributed to HIV. In contrast, the Maternal Mortality Estimation Interagency Group (MMEIG) estimated that only 5.9% of maternal deaths were due to HIV/AIDS globally.(31) 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 among HIV-infected pregnant and postpartum woman are classified as maternal deaths whereas 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 article we report data on the risk ratio and the prevalence of HIV from a systematic review of studies that compare mortality during pregnancy and the postpartum in HIV-infected and HIV-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 (PAFs) for each study individually and under scenarios of varying HIV prevalence using the pooled risk ratio obtained from the meta-analysis.

3.2.3 Methods

Search strategy

A review protocol outlining the methods for our systematic review was developed and reviewed by external experts (Appendix A, page 234). We searched bibliographical databases (PubMed, EMBASE, Popline) and a WHO regional database [African Index Medicus (AIM)] on 6 July 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 Appendix B (page 243). 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 (C.C.) and full texts were sought for relevant articles. A 20% sample of the titles and abstracts was screened by a second reviewer to crosscheck 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 HIV-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).(16) 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-based or facility-based. Conference abstracts were excluded.

Data extraction

Data for each study were extracted by a single author (C.C.) 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 in which 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.(102) Where data on the prevalence of HIV or ART availability among pregnant women were not available from the published article, estimates were obtained from the Joint United Nations Programme on HIV/AIDS (UNAIDS) for the same time period and region or country. Data duplicated in different articles were only extracted once.

Assessment of the risk of bias

The risk of bias for each study was assessed according to the following criteria:

1. 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.
2. Adjustment for confounders: Inadequate if there was no adjustment for confounders or if there was no attempt to match HIV-infected and HIV-uninfected women on potential confounders.
3. Definition of pregnancy-related death: Inadequate if the time period in which women were observed was not stated or unclear.
4. 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).
5. 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 HIV-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, attributable risk and PAF were calculated.(88)

A meta-analysis was conducted using Stata 12.0 (Stata Corp., College Station, Texas, USA) to calculate both the pooled risk ratio and pooled attributable risk quantifying the increased risk of a pregnancy-related death in HIV-infected women compared with HIV-uninfected women. Given the variation in study design the DerSimonian–Laird random effects method was used to combine study estimates.(87) 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 risk ratio for the association between HIV and pregnancy-related mortality. Meta-analyses were conducted for each quality criterion outlined previously, stratifying the pooled risk ratio by whether studies 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 risk ratio obtained from the meta-analysis according to the following formula:

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

where p is the prevalence of HIV and RR is the pooled risk ratio.

3.2.4 Results

Figure 3.1 quantifies the number of studies excluded at each stage of the review process. Eighteen thousand, nine hundred and forty-nine 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 HIV-uninfected women.

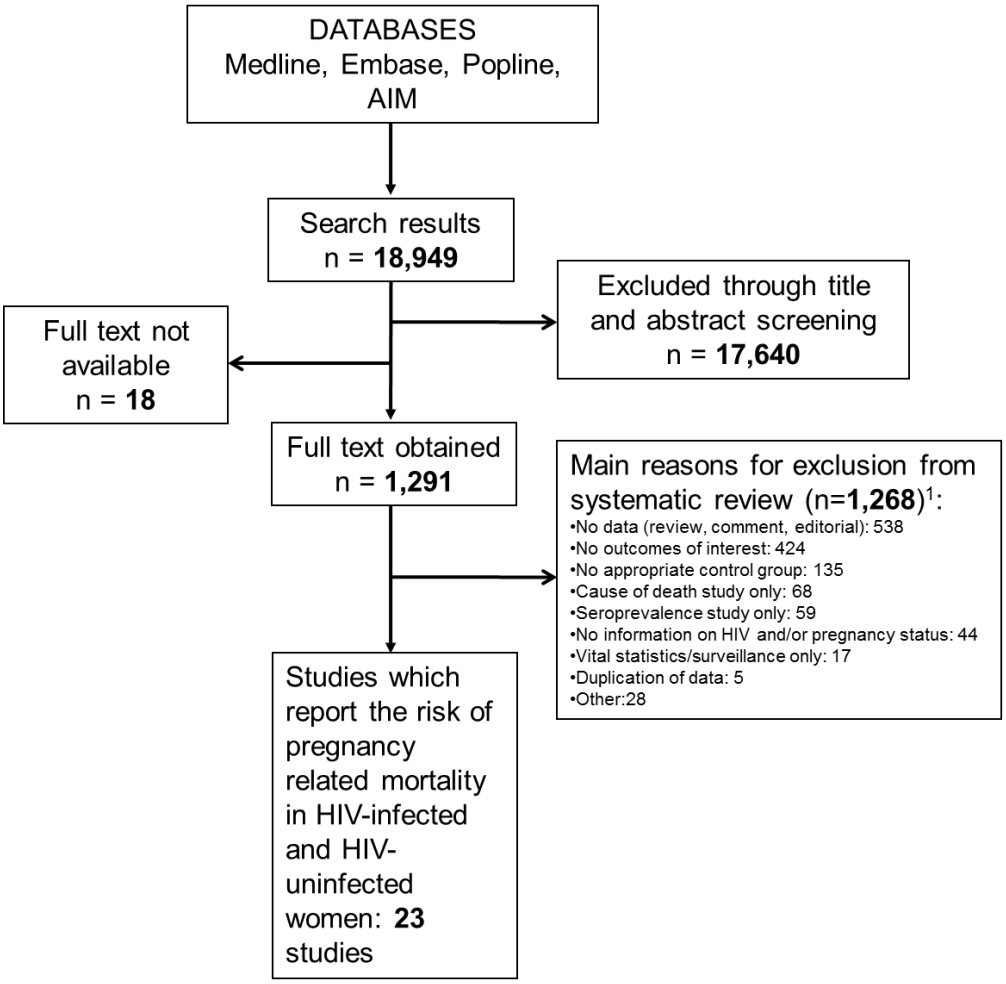

Figure 3.1: Flow chart of study selection for inclusion in the systematic review
[1] Articles may have been excluded for multiple reasons

A description of the 23 eligible studies is contained in Table 3.3 (page 55). Study populations were from South Africa,(20, 103, 104) Tanzania,(105) Republic of Congo,(106) Democratic Republic of Congo,(107) Malawi,(108) Zimbabwe,(73, 109, 110) Rwanda,(59, 111) Uganda,(112-114) Kenya,(115) India,(116, 117) Spain,(65) USA,(118, 119) and Mexico.(120) One study included women from two different countries (Malawi and Zambia).(121) 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 (120) and three studies did not follow women during pregnancy: women were followed from delivery to 15 days postpartum;(111) from active labour to one year postpartum (107) and from within 96 hours of delivery to one year postpartum.(110) The remaining eight studies did not provide sufficient information on the timing during pregnancy and the postpartum period. Two studies were population-based,(106, 114) 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 (103) and the other recruited women who were admitted to hospital in pregnancy during seasonal

outbreaks of malaria.(73) Two studies included women only having caesarean sections.(65, 119)

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 [risk ratio: 0.33, 95% confidence interval (95% CI): 0.01–8.17].(111) This study was small, only picking up one pregnancy-related death. Meta-analysis of the risk ratio from the 23 studies indicated that HIV-infected women had eight times the risk of a pregnancy-related death compared with uninfected women (pooled risk ratio: 7.74, 95% CI: 5.37–11.16) (Figure 3.2). There was strong evidence for between-study heterogeneity (I^2=54.1%, p=0.001).

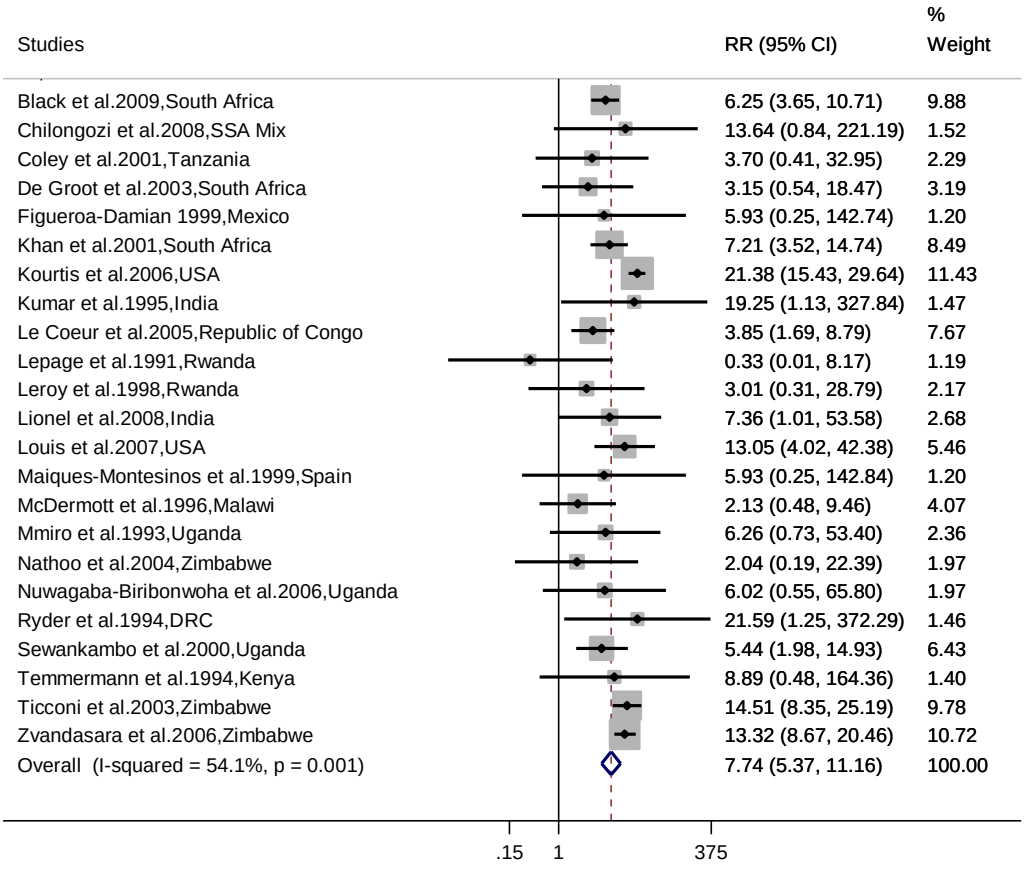

Figure 3.2: Forest plot showing the strength of association between HIV and pregnancy-related mortality
Abbreviations: SSA=sub-Saharan Africa; DRC=Democratic Republic of Congo

The results of the stratified meta-analyses are presented in Table 3.1. No clear patterns emerged. In East Africa, where the majority of the studies were conducted, the risk ratio was 7.21 (95% CI: 4.36–11.92). Higher risk ratios were found in the United States and South Asia, but there were only two studies in each of these regions. The

pooled risk ratio 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 risk ratio than the 20 facility-based studies [4.42 (95% CI: 2.23–8.38) and 8.70 (95% CI: 5.99–12.62) respectively].

Table 3.1: 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	4	11.47 (7.99-16.48)	0	0.52
Unclear	8	11.68 (7.19-18.97)	44.4	0.08

Abbreviations: CI=confidence interval

Studies using a definition which included the period beyond 42 days postpartum had more than double the pooled risk ratio (11.47, 95% CI: 7.99–16.48) compared with those which only pertained to pregnancy, delivery or up to 42 days postpartum (4.78, 95% CI: 3.23–7.06) (Table 3.1). Studies which did not provide a clear definition of the follow-up period also had a high pooled risk ratio of 11.68 (95% CI: 7.19–18.97). Although there was still weak evidence for between-study heterogeneity among 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 Table 3.4 (page 63). Overall, most of the studies were judged to be of inadequate quality for at least one of the quality criteria. The pooled risk ratio, stratified by whether the study was judged to be of

adequate quality for each quality criterion are presented in Table 3.2. 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 risk ratio 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 among women who were HIV-infected (attributable risk) ranged from 174 per 100,000 pregnant women in South Africa (104) to 28 386 per 100,000 pregnant women in Zimbabwe (73) (Table 3.3). Overall, the pooled attributable risk 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).

Table 3.2: 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)

Abbreviations: CI=confidence interval

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 (65) to 78.7% in a study from Zimbabwe (110) (Table 3.3, Figure 3.3).

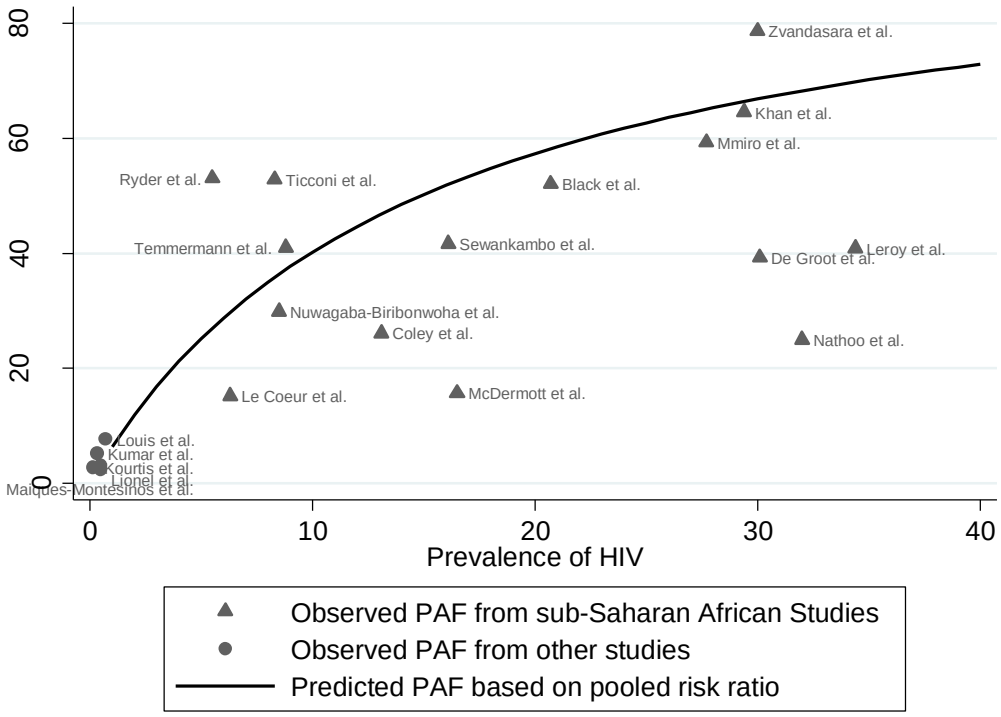

Figure 3.3: The population attributable fraction (PAF) for the proportion of deaths attributable to HIV amongst pregnant/postpartum women. Individual data points show the observed PAF for each study and the curve shows the PAF predicted using the pooled risk ratio from all the studies.

Individual PAFs exceeded 40% in studies from South Africa,(20, 104) Zimbabwe,(73, 110) Rwanda,(59) Uganda,(112, 114) the Democratic Republic of Congo,(107) and Kenya.(115) Using the summary risk ratio of 7.74, we calculated the PAF for varying prevalences of HIV (Figure 3.3). For a region where the HIV prevalence is 2% among 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%.

3.2.5 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 attributable risk 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.(122) On the basis of 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,(123) and pregnant HIV-infected women are thought to be healthier than non-pregnant HIV-infected women.(106, 124) In two population-based studies the excess mortality attributable to HIV was much smaller in pregnant than in non-pregnant HIV-infected women.(106, 114) 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.

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 HIV-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 risk ratio. Consequently, the summary estimate obtained should be interpreted as an average risk ratio about which the true study risk ratios actually vary. Previous estimates of the proportion of maternal deaths that are attributable to HIV, on the contrary, 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.(28, 29) The MMEIG model uses a more complex model based on two key

assumptions: the proportion of AIDS deaths among all women of reproductive that occur to pregnant women and the proportion of pregnancy-related deaths to HIV-infected women that qualify as maternal deaths.(31, 32) As 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 woman 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 categorized 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).(16) 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.(17) Conditions such as severe anaemia and tuberculosis 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 risk ratio 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.(110) 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 because we had no data on the proportion of individuals on ART. No studies

adjusted any of the risk ratios for confounders, although several studies did match the HIV-infected and HIV-uninfected women on age and parity and one study also matched the women on socioeconomic status. Consequently, the PAFs we estimate for varying prevalences of HIV, which are mostly based on crude risk ratio, may have been overestimated.

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 risk ratio 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 HIV-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 Millennium Development Goal 5 – 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.

Table 3.3: Summary of studies of HIV and pregnancy-related mortality

Reference	Study design	Study Setting	Study Population	ART Available	Prevalence of HIV[2]	Definition of pregnancy-related mortality[3]	Risk of pregnancy-related death amongst HIV+ women per 100,000 women *(total number of HIV+ women)*	Risk of pregnancy-related death amongst HIV- women per 100,000 women *(total number of HIV- women)*	Risk Ratio (95% CI)	Attributable Risk per 100,000 women (95% CI)	Population Attributable Fraction
Black *et al.*, 2009(20)	Retrospective Cohort	A single tertiary hospital in Johannesburg, South Africa (2003-2007)	All women with known HIV status who gave birth; any maternal deaths during pregnancy until 42 days postpartum included	Both	20.7%	Maternal Death	776[4] *(7,605)*	124[4] *(13,694)*	6.25 (3.65-10.71)	652 (446-857)	52.1%
Chilongozi *et al.*, 2008(121)	Prospective Cohort (from an RCT)	Multiple hospitals and antenatal clinics in Malawi (Blantyre and Lilongwe) and Zambia (Lusaka) (2001-2003)	All HIV+ women enrolled and 1 HIV- woman enrolled for every 5 HIV+ women; followed up from between 20 and 24 weeks of pregnancy to 12 months postpartum	No	NA	Pregnancy-related death	1824 *(1,864)*	0 *(367)*	13.64 (0.84-221.19)	1832 (1164-2501)	NA
Coley *et al.*, 2001(105)	Prospective Cohort	Three hospitals and one clinic in Dar es Saalam, Tanzania (1995-1997)	HIV+ women recruited from control arm of an RCT and HIV- women from psychosocial study; followed up from between 12 and 27 weeks of pregnancy until delivery	No[1]	13.1%	Pregnancy-related death	760 *(526)*	206 *(486)*	3.70 (0.41-32.95)	555 (-290-1399)	26.1%

Reference	Study design	Study Setting	Study Population	ART Available	Prevalence of HIV[2]	Definition of pregnancy-related mortality[3]	Risk of pregnancy-related death amongst HIV+ women per 100,000 women *(total number of HIV+ women)*	Risk of pregnancy-related death amongst HIV- women per 100,000 women *(total number of HIV- women)*	Risk Ratio (95% CI)	Attributable Risk per 100,000 women (95% CI)	Population Attributable Fraction
De Groot *et al.*, 2003(103)	Retrospective Cohort	A single high risk obstetric unit in Bloemfontein, South Africa (2001)	All HIV+ women and 2 HIV- controls for every HIV+ women enrolled from a high risk obstetric unit; all information extracted from medical records and no information on follow-up time given	No[1]	30.1% in 2001 in Free State Province [a]	"Maternal death", unclear	3704 *(81)*	1176 *(170)*	3.15 (0.54-18.47)	2528 (-1893-6948)	39.3%
Figueroa-Damian, 1999(120)	Prospective Cohort	Institute of Perinatology in Mexico City, Mexico (1989-1997)	44 HIV+ women and 2 controls for every HIV+ women, match on age and socioeconomic status; followed up from enrolment in pregnancy to the end of delivery	Both	No estimate available	"Maternal death", unclear	2273 *(44)*	0 *(88)*	5.93 (0.25-142.74)	2273 (-3197-7742)	NA
Khan *et al.*, 2001(104)	Retrospective Cohort	A single tertiary hospital in Durban, South Africa (1996-1998)	Total number of deliveries to HIV+ and HIV- women was calculated based on reported HIV prevalence and no. of deliveries in hospital; HIV status of maternal deaths (up to 1 year postpartum) known through HIV tests	No[1]	29.4%	Maternal death (including late maternal deaths)	202 *(14,849)*	280 *(35,669)*	7.21 (3.52-14.74)	174 (100-248)	64.6%

Reference	Study design	Study Setting	Study Population	ART Available	Prevalence of HIV[2]	Definition of pregnancy-related mortality[3]	Risk of pregnancy-related death amongst HIV+ women per 100,000 women *(total number of HIV+ women)*	Risk of pregnancy-related death amongst HIV- women per 100,000 women *(total number of HIV- women)*	Risk Ratio (95% CI)	Attributable Risk per 100,000 women (95% CI)	Population Attributable Fraction
Kourtis *et al.*, 2006(118)	Retrospective Cohort	20% of all community hospitals in the USA (1994 and 2003)	All HIV+ and HIV- pregnant women between 15-44 years of age who were hospitalised; all information extracted from medical records and no information on follow-up time given	Yes	0.14%	Pregnancy-related death	299 *(12,378)*	14 *(8,784,767)*	21.38 (15.43-29.64)	285 (189-381)	2.8%
Kumar *et al.*, 1995(116)	Prospective Cohort	A single tertiary hospital in Manipur, India (1992-1993)	160 HIV+ women and 160 HIV- mothers (matched for age and parity); followed up from less than 28 weeks of pregnancy to 42 days postpartum	No	0.3% in 1992 in all urban areas of India [b] [2]	Maternal death	6000 *(150)*	0 *(152)*	19.25 (1.13-327.84)	6000 (2023-9977)	5.2%
Le Coeur *et al.*, 2005(106)	Census	Pointe Noire, Republic of Congo (2001)	Total number of deliveries to HIV+ and HIV- women was calculated based on the total number of live and still births and assuming a HIV prevalence 6.3%; HIV status of maternal deaths (up to 42 days postpartum) known through HIV tests	No[1]	6.3%	Pregnancy-related	1813 *(386)*	471 *(5734)*	3.85 (1.69-8.79)	1343 (0-2686)	15.2%

Reference	Study design	Study Setting	Study Population	ART Available	Prevalence of HIV[2]	Definition of pregnancy-related mortality[3]	Risk of pregnancy-related death amongst HIV+ women per 100,000 women *(total number of HIV+ women)*	Risk of pregnancy-related death amongst HIV- women per 100,000 women *(total number of HIV- women)*	Risk Ratio (95% CI)	Attributable Risk per 100,000 women (95% CI)	Population Attributable Fraction
Lepage *et al.* 1991(111)	Prospective Cohort	A single hospital in Kigali, Rwanda (1988-1989)	All HIV+ women and an equal number of HIV- women matched for age and parity. Women had to have lived for at least 6 months in a district within a diameter of <10 Km from the hospital and delivered a live newborn; follow-up from delivery to 15 days postpartum	No	30.3%	Maternal death	0 *(215)*	463[4] *(216)*	0.33 (0.01-8.17)	-463 (-1738-812)	NA
Leroy *et al*,1998(59)	Prospective Cohort	A single tertiary hospital in Kigali, Rwanda (1992-1993)	All HIV+ women and an equivalent number of HIV- women matched for age who attended the antenatal clinic for 2 days each week, who were resident in Kigali and who wished to deliver in the hospital; followed up from 21-28 weeks of gestation to 42 days postpartum	No	34.4%	Pregnancy-related	824 *(364)*	274 *(365)*	3.01 (0.31-28.79)	550 (-522-1623)	40.9%
Lionel *et al*, 2008(117)	Retrospective Cohort	A single hospital in Vellore, India (2000-2002)	All HIV+ and HIV- women; all information extracted from medical records and no information on follow-up time given	Yes	0.5%	"Maternal death", unclear	917 *(109)*	125 *(23,277)*	7.36 (1.01-53.58)	793 (-998-2583)	3.1%

Reference	Study design	Study Setting	Study Population	ART Available	Prevalence of HIV[2]	Definition of pregnancy-related mortality[3]	Risk of pregnancy-related death amongst HIV+ women per 100,000 women *(total number of HIV+ women)*	Risk of pregnancy-related death amongst HIV- women per 100,000 women *(total number of HIV- women)*	Risk Ratio (95% CI)	Attributable Risk per 100,000 women (95% CI)	Population Attributable Fraction
Louis *et al.*, 2007(119)	Prospective Cohort	19 different academic medical centres in the USA (1999-2002)	All women having a c-section with a gestational age of >20 weeks at delivery and who delivered an infant of at least 500g birth weight with known HIV status; only look at mortality around delivery	Yes[1]	0.69%	"Maternal death", unclear	794 *(378)*	61 *(54,281)*	13.05 (4.02-42.38)	733 (-162-1628)	7.7%
Maiques-Montesinos *et al.*, 1999(65)	Retrospective Cohort	A single maternity hospital in Valencia, Spain (1987-1996)	All HIV+ women having a c-section and a sample of HIV- women undergoing c-section matched for indication for c-section, stage of labour, number of foetuses and date of delivery; all information extracted from medical records and no information on follow-up time given	No	0.49%	"Maternal death", unclear	2222 *(45)*	0 *(90)*	5.93 (0.25-142.84)	2222 (-3130-7575)	2.4%
McDermott *et al.*, 1996(108)	Prospective Cohort	Four antenatal clinics in Mangochi District, Malawi (1987-1989)	All HIV+ and HIV- women; followed up from their first antenatal visit to 6 weeks postpartum	No[1]	16.5% in 1994 [c][2]	Pregnancy-related	735 *(272)*	346 *(3,472)*	2.13 (0.48-9.48)	390 (-644-1424)	15.7%

Reference	Study design	Study Setting	Study Population	ART Available	Prevalence of HIV[2]	Definition of pregnancy-related mortality[3]	Risk of pregnancy-related death amongst HIV+ women per 100,000 women *(total number of HIV+ women)*	Risk of pregnancy-related death amongst HIV- women per 100,000 women *(total number of HIV- women)*	Risk Ratio (95% CI)	Attributable Risk per 100,000 women (95% CI)	Population Attributable Fraction
Mmiro *et al.*, 1993(112)	Prospective Cohort	A University hospital in Kampala, Uganda (1988-1990)	All HIV+ women and a random 10% sample of HIV- women who lived within 15km of Mulago and agree to deliver in the hospital; followed up from pregnancy until discharge after delivery	No[1]	27.7%	Pregnancy-related	898 *(557)*	143 *(697)*	6.26 (0.73-53.40)	754 (-78-1586)	59.3%
Nathoo *et al.*, 2004(109)	Prospective Cohort	A single tertiary hospital in Harare, Zimbabwe (1991-1995)	384 HIV+ women and 374 HIV- mothers (matched for age) enrolled; followed up from delivery to 6 weeks postpartum	No[1]	32.0% in 1995 [d] [2]	Pregnancy-related	562 *(356)*	275 *(363)*	2.04 (0.19-22.39)	286 (-659-1232)	25.0 %
Nuwagaba-Biribonwoha *et al.*, 2006(113)	Prospective Cohort	A single hospital in Kampala, Uganda (2002-2004)	132 HIV+ and 399 HIV- nulliparous and uniparous women enrolled; followed up from 36 weeks of pregnancy to 6 weeks postpartum	Yes	8.5% in 2002 [e] [2]	Pregnancy-related	1527 *(131)*	254 *(394)*	6.02 (0.55-65.80)	1273 (-885-3431)	29.9%
Ryder *et al.*, 1994(107)	Prospective Cohort	A single hospital in Kinshasa, Democratic Republic of Congo (1986-1987)	All HIV+ women, and a sample of HIV- women matched for age and parity to each HIV+ women recruited; followed up from active labour to 1 year postpartum	No[1]	5.5%	Pregnancy-related	3239 *(247)*	0 *(314)*	21.59 (1.25-372.30)	3239 (932-5545)	53.1%

Reference	Study design	Study Setting	Study Population	ART Available	Prevalence of HIV[2]	Definition of pregnancy-related mortality[3]	Risk of pregnancy-related death amongst HIV+ women per 100,000 women *(total number of HIV+ women)*	Risk of pregnancy-related death amongst HIV- women per 100,000 women *(total number of HIV- women)*	Risk Ratio (95% CI)	Attributable Risk per 100,000 women (95% CI)	Population Attributable Fraction
Sewankambo *et al.*, 2000(114)	Prospective Cohort	Rakai, Uganda (1994-1997)	All households in 56 communities located on secondary roads eligible for inclusion in cohort and HIV tests; continuous follow-up, but not clear what time period women were considered at risk of "maternal death"	No	16.1%	"Maternal death", unclear	1687 *(415)*	310 *(2,582)*	5.44 (1.98-14.93)	1377 (120-2634)	41.7%
Temmermann *et al.*, 1994(115)	Prospective Cohort	A single health centre in Nairobi, Kenya (1989-1991)	All HIV+ women, and a sample of HIV- women matched for age and parity to each HIV+ women recruited; followed up from less than 28 weeks of pregnancy to 6 weeks postpartum	No[1]	8.8%	Pregnancy-related	1269 *(315)*	0 *(311)*	8.89 (0.48-164.36)	1270 (-110-2650)	41.0%
Ticconi *et al.*, 2003(73)	Retrospective Cohort	A single tertiary hospital in Centenary Zimbabwe (2000-2001)	All woman with known HIV status; followed up from discharge from hospital during pregnancy to the end of pregnancy	No[1]	8.3%	"Maternal death", unclear	30488 *(82)*	2102 *(904)*	14.51 (8.35-25.19)	28386 (18378-38394)	52.9%

Reference	Study design	Study Setting	Study Population	ART Available	Prevalence of HIV[2]	Definition of pregnancy-related mortality[3]	Risk of pregnancy-related death amongst HIV+ women per 100,000 women *(total number of HIV+ women)*	Risk of pregnancy-related death amongst HIV- women per 100,000 women *(total number of HIV- women)*	Risk Ratio (95% CI)	Attributable Risk per 100,000 women (95% CI)	Population Attributable Fraction
Zvandasara *et al.*, 2006(110)	Prospective Cohort (from an RCT)	14 maternity clinics and hospitals in Greater Harare, Zimbabwe (1997-2000)	All HIV+ and HIV- women were recruited if neither they or their baby had a life-threatening condition, the baby was not from a multiple birth or had a birth weight<1500g; followed up from within 96 hours of delivery to 1 year postpartum	No[1]	30.0% in 2000 [d] [2]	Pregnancy-related	3726 *(3,999)*	280 *(8,577)*	13.32 (8.67-20.46)	3446 (2849-4044)	78.7%

[1]Information was not supplied in the published paper so whether antiretroviral treatment should have been available was based on the study dates and study location; for two studies it was not clear from the study dates and location whether ART would be available so the information was inferred from the literature.

- **a) Pointe Noire, Congo in 2001: No ART treatment based on the UNAIDS data accessed on 31st May 2012 at http://www.unaids.org/en/regionscountries/countries/democraticrepublicofthecongo/**
- **b) Greater Harare, Zimbabwe in 2000: No ART treatment based on the UNAIDS data accessed on 31st May 2012 at http://www.unaids.org/en/regionscountries/countries/zimbabwe/**
- **c) Bloemfontein, South Africa in 2001: No ART treatment based on the UNAIDS data accessed on 7th July 2012 at http://www.unaids.org/en/regionscountries/countries/southafrica/**

[2]Sources of HIV prevalence, when this information was not provided in the paper:

- **a) UNAIDS. South Africa: Epidmiological Factsheets on HIV/AIDs and Sexually Transmitted Infections 2004.**
- **b) UNAIDS. India: Epidmiological Factsheets on HIV/AIDs and Sexually Transmitted Infections 2004.**
- **c) UNAIDS. Malawi: Epidmiological Factsheets on HIV/AIDs and Sexually Transmitted Infections 2004.**
- **d) UNAIDS. Zimbabwe: Epidmiological Factsheets on HIV/AIDs and Sexually Transmitted Infections 2004.**
- **e) UNAIDS. Uganda: Epidmiological Factsheets on HIV/AIDs and Sexually Transmitted Infections 2004.**

[3]Definition of maternal death classified as" maternal death" if incidental deaths were excluded; as "pregnancy-related" if incidental deaths were not excluded or they only used the term death and as "Maternal death, unclear" if they use the term maternal death but do not define this in the paper

[4]Use number of live births as dominator rather than number of women

Table 3.4: Methodological quality assessment for each of the studies included in the systematic review

Reference	Quality Criteria				
	Loss to follow up	**Adjustment for confounders**	**Definition of pregnancy-related death**	**Ascertainment of maternal death**	**Selection of comparison group**
Black *et al.*, 2009(20)	**Inadequate:** 28% of deaths had known HIV status	**Inadequate:** No adjustment for confounders	**Adequate:** All deaths of women at the facility during pregnancy or within 42 days of childbirth	**Inadequate:** Hospital record review	**Adequate:** Include all women with known HIV status for a single facility
Chilongozi *et al.*, 2008(121)	**Adequate:** Less than 10% of HIV+ and HIV- women loss to follow-up	**Inadequate:** No adjustment for confounders	**Adequate:** All pregnancy-related deaths up to one year postpartum	**Adequate:** Prospective cohort study	**Inadequate:** Unclear on exact selection methods; however no HIV-women were selection from one of the study sites
Coley *et al.*, 2001(105)	**Adequate:** Less than 10% of HIV+ and HIV- women loss to follow-up	**Inadequate:** No adjustment for confounders	**Adequate:** Any death before delivery	**Adequate:** Prospective cohort study	**Inadequate:** HIV+ and HIV- women were recruited from different studies
De Groot *et al.*, 2003(103)	**Adequate:** 53 (17%) women were excluded after study groups were selected (due to HIV status unknown (n=6), discharge before delivery (n=45) and abortion (n=2))	**Inadequate:** No adjustment for confounders	**Inadequate:** No information on the period of pregnancy in which women were observed	**Inadequate:** Hospital record review	**Adequate:** HIV+ and HIV- women enrolled from the same study site
Figueroa-Damian, 1999(120)	**Inadequate:** Insufficient information provided	**Adequate:** Match for age and socio-economic status	**Adequate:** Any death before delivery	**Adequate:** Prospective cohort study	**Inadequate:** Unclear on exact selection methods; HIV-infected women were recruited from a Department of Infectious Diseases, but do not state where HIV-uninfected women were recruited from
Khan *et al.*, 2001(104)	**Inadequate:** Over 50% of deaths had unknown HIV status	**Inadequate:** No adjustment for confounders	**Adequate:** All deaths of women at the facility during pregnancy or within 1 year of childbirth	**Inadequate:** Hospital record review	**Adequate:** Include all women with known HIV status for a single facility
Kourtis *et al.*, 2006(118)	**Inadequate:** Insufficient information provided	**Inadequate:** No adjustment for confounders	**Inadequate:** No information on the period of pregnancy in which women were observed	**Inadequate:** Hospital discharge data from national database	**Adequate:** Include all hospitalised, pregnant women with known HIV status
Kumar *et al.*, 1995(116)	**Adequate:** Less than 10% of HIV+ and HIV- women loss to follow-up	**Adequate:** Match for age and parity	**Adequate:** Maternal deaths up to 42 days postpartum	**Adequate:** Prospective cohort study	**Adequate:** HIV+ and HIV- women enrolled from the same study site
Le Coeur *et al.*, 2005(106)	**Adequate:** Over 90% of deaths had known HIV status	**Inadequate:** No adjustment for confounders[1]	**Adequate:** All pregnancy-related deaths up to 42 days postpartum	**Adequate:** All deaths identified in city mortuary	**Adequate:** Capture all women in Pointe Noire
Lepage *et al.* 1991(111)	**Inadequate:** Between delivery and 15 days	**Adequate:** Match for age and parity	**Adequate:** All pregnancy-related deaths up to 42 days postpartum	**Adequate:** Prospective cohort study	**Adequate:** HIV+ and HIV- women enrolled from the same study site

Reference	Quality Criteria				
	Loss to follow up	**Adjustment for confounders**	**Definition of pregnancy-related death**	**Ascertainment of maternal death**	**Selection of comparison group**
	postpartum 21% of HIV+ women were lost to follow-up				
Leroy *et al*,1998(59)	**Adequate:** Less than 10% of HIV+ and HIV- women loss to follow-up	**Adequate:** Match for age and parity	**Adequate:** All pregnancy-related deaths up to 42 days postpartum	**Adequate:** Prospective cohort study	**Adequate:** HIV+ and HIV- women enrolled from the same study site
Lionel *et al*, 2008(117)	**Inadequate:** Insufficient information provided	**Inadequate:** No adjustment for confounders	**Inadequate:** No information on the period of pregnancy in which women were observed	**Inadequate:** Hospital record review	**Adequate:** All women from study hospital enrolled
Louis *et al.*, 2007(119)	**Inadequate:** Insufficient information provided	**Inadequate:** No adjustment for confounders	**Inadequate:** No information on the period of pregnancy in which women were observed	**Inadequate:** Data came from the Maternal-Fetal Medicine Units Network Caesarean registry	**Adequate:** All women enrolled
Maiques-Montesinos *et al.*, 1999(65)	**Inadequate:** Insufficient information provided	**Inadequate:** No adjustment for confounders	**Inadequate:** No information on the period of pregnancy in which women were observed	**Inadequate:** Hospital record review	**Adequate:** HIV+ and HIV- women enrolled from the same study site
McDermott *et al.,* 1996(108)	**Adequate:** Less than 10% of HIV+ and HIV- women loss to follow-up	**Inadequate:** No adjustment for confounders	**Adequate:** All pregnancy-related deaths up to 42 days postpartum	**Adequate:** Prospective cohort study	**Adequate:** All women enrolled
Mmiro *et al.,* 1993(112)	**Inadequate:** Insufficient information provided	**Inadequate:** No adjustment for confounders	**Inadequate:** States that woman were followed up through pregnancy until discharge after delivery –insufficient information.	**Adequate:** Prospective cohort study	**Adequate:** HIV+ and HIV- women enrolled from the same study site
Nathoo *et al.,* 2004(109)	**Adequate:** Less than 10% of HIV+ and HIV- women loss to follow-up	**Adequate:** Match for age	**Adequate:** All pregnancy-related deaths up to 42 days postpartum	**Adequate:** Prospective cohort study	**Adequate:** All women enrolled before being tested for HIV
Nuwagaba-Biribonwoha *et al.*, 2006(113)	**Adequate:** Less than 10% of HIV+ and HIV- women loss to follow-up	**Inadequate:** No adjustment for confounders	**Adequate:** All pregnancy-related deaths up to 42 days postpartum	**Adequate:** Prospective cohort study	**Adequate:** HIV+ and HIV- women enrolled from the same hospital
Ryder *et al.*, 1994(107)	**Inadequate:** More than 20% of HIV+ women loss to follow-up	**Adequate:** Match for age and parity	**Adequate:** All pregnancy-related deaths up to one year postpartum	**Adequate:** Prospective cohort study	**Adequate:** HIV+ and HIV- women enrolled from the same hospital
Sewankambo *et al.*, 2000(114)	**Inadequate:** About 25% of the study cohort loss to follow-up	**Inadequate:** No adjustment for confounders	**Inadequate:** No information on the period of pregnancy in which women were observed	**Inadequate:** Death data collected from household census; not clear how data on pregnancy was collected	**Adequate:** All women from study area enrolled
Temmermann *et al.*, 1994(115)	**Inadequate:** More than 20% of HIV+ and HIV- women loss to follow-up	**Adequate:** Match for age and parity	**Adequate:** All pregnancy-related deaths up to 42 days postpartum	**Adequate:** Prospective cohort study	**Adequate:** HIV+ and HIV- women enrolled from the same antenatal clinics

Reference	Quality Criteria				
	Loss to follow up	**Adjustment for confounders**	**Definition of pregnancy-related death**	**Ascertainment of maternal death**	**Selection of comparison group**
Ticconi *et al.*, 2003(73)	**Inadequate:** Insufficient information provided	**Inadequate:** No adjustment for confounders	**Inadequate:** No information on the period of pregnancy in which women were observed	**Adequate:** Prospective cohort study	**Adequate:** All women with known HIV status enrolled from study hospital
Zvandasara *et al.*, 2006(110)	**Adequate:** Just over 10% of HIV+ and HIV- women loss to follow-up	**Inadequate:** No adjustment for confounders	**Adequate:** All pregnancy-related deaths up to one year postpartum	**Adequate:** Prospective cohort study	**Adequate:** All women enrolled before being tested for HIV

[1]**This study presented the adjusted the rate ratio comparing mortality rates in HIV-infected with uninfected for age; however, to enable the data to be pooled with the other studies information was only extracted on the risk ratio, using number of pregnant women for the denominator, rather than number of women years**

3.3 CONCLUSION

The results of this published paper show that in areas with high HIV prevalence, the percentage of pregnancy-related mortality attributable to HIV is substantial. Whether this excess mortality reflects the coexistence of HIV in pregnant women (i.e. HIV is a coincidental cause of death in pregnancy), or whether this excess is due to an acceleration of HIV disease (i.e. HIV is an indirect cause of death) or an increased risk of obstetric complications in HIV-infected pregnant women is unclear.

Chapter 5 and Chapter 6 aim to shed light on the possible mechanisms which may lead to this excess mortality, while Chapter 7 will adopt a similar methodology as that used in this paper to calculate the excess pregnancy-related mortality attributable to HIV using population-based data from Eastern and Southern Africa.

4 HIV AND THE RISK OF DIRECT OBSTETRIC COMPLICATIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

4.1 INTRODUCTION

Presented in this chapter are the results of the second systematic review which aimed to address the second objective of this PhD, establishing whether HIV increases the risk of direct obstetric complications. These results were published in PLOS One in October 2013 (see (125) for published version of the paper) and formed part of a Maternal Health Task Force-PLOS collection themed “Maternal Health is Women’s Health”.(126)

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I am the first author on this paper. I was responsible for the research design, undertaking the systematic review and conducting the meta-analysis. I was also primarily responsible for writing this work. My co-author supported this work in an advisory capacity and helping to edit the writing.

NAME IN FULL (Block Capitals) CLARA CALVERT

STUDENT ID NO: 236162

CANDIDATE'S SIGNATURE ……..…….
Date

SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above)

……..……

4.2 ARTICLE

4.2.1 Abstract

Background: Women of reproductive age in parts of sub-Saharan Africa are faced both with high levels of HIV and the threat of dying from the direct complications of pregnancy. Clinicians practicing in such settings have reported a high incidence of direct obstetric complications among HIV-infected women, but the evidence supporting this is unclear. The aim of this systematic review is to establish whether HIV-infected women are at increased risk of direct obstetric complications.

Methods and findings: Studies comparing the frequency of obstetric haemorrhage, hypertensive disorders of pregnancy, dystocia and intrauterine infections in HIV-infected and uninfected women were identified. Summary estimates of the odds ratio (OR) for the association between HIV and each obstetric complication were calculated through meta-analyses. In total, 44 studies were included providing 66 data sets; 17 on haemorrhage, 19 on hypertensive disorders, five on dystocia and 25 on intrauterine infections. Meta-analysis of the OR from studies including vaginal deliveries indicated that HIV-infected women had over three times the risk of a puerperal sepsis compared with HIV-uninfected women [pooled OR: 3.43, 95% confidence interval (CI): 2.00-5.85]; this figure increased to nearly six amongst studies only including women who delivered by caesarean (pooled OR: 5.81, 95% CI: 2.42-13.97). For other obstetric complications the evidence was weak and inconsistent.

Conclusions: The higher risk of intrauterine infections in HIV-infected pregnant and postpartum women may require targeted strategies involving the prophylactic use of antibiotics during labour. However, as the huge excess of pregnancy-related mortality in HIV-infected women is unlikely to be due to a higher risk of direct obstetric complications, reducing this mortality will require non obstetric interventions involving access to ART in both pregnant and non-pregnant women.

4.2.2 Introduction

The substantial burden of HIV infection amongst women of reproductive age in sub-Saharan Africa and the maternal health risks that these women are challenged with has led to HIV and maternal mortality being described as two intersecting epidemics.(5, 127) Many pregnant women in this region face not only the threat of dying from the direct complications of pregnancy and delivery, but also from complications arising

from advancing HIV disease. Given this intersection, it is important to understand whether and how HIV interacts with pregnancy.

The biological interaction between HIV and pregnancy is not well understood. It has been argued that pregnancy may accelerate HIV progression as pregnancy is associated with suppressed immune function independent of HIV status.(128, 129) However, the epidemiological evidence supporting this hypothesis is weak. A systematic review investigating the effects of pregnancy on HIV progression and survival found no evidence that pregnancy increased progression to an HIV-related illness or a fall in CD4 count to fewer than 200 cells per cubic millilitre. The same review showed weak evidence that pregnant women were more likely to progress to an AIDS-defining illness or death compared with their non-pregnant counterparts but this was based on only six studies.(51)

Clinicians working in settings where HIV is highly prevalent have reported a high incidence of direct obstetric complications in HIV-infected pregnant women.(130) Some researchers have also hypothesised that HIV may increase the risk of direct obstetric complications, though the evidence was based on very few studies with small sample sizes.(5, 131) There are several biological pathways which may explain such an association. Firstly, the compromised immune status and general poor health of HIV-infected women may leave them more vulnerable to infections, including puerperal sepsis.(6) Secondly, it has been suggested that HIV-related thrombocytopenia, where there is a low platelet count in the blood, may increase a woman's risk of haemorrhage.(56) Additionally, social factors such as poor access to healthcare increase a woman's risk of obstetric complications, and may be exacerbated in HIV-infected women due to the discrimination and stigma these women face in some settings.(57)

To date there has been no effort to synthesise the empirical evidence on the association between HIV and direct obstetric complications. The aim of this study is to investigate whether HIV increases the risk of obstetric complications, by systematically reviewing literature which compares the risk of obstetric complications in HIV-infected and uninfected women. The obstetric complications which were pre-specified for this review are obstetric haemorrhage, pregnancy-induced hypertension, dystocia and intrauterine infections.

4.2.3 Methods

Search Strategy

Pubmed, Embase, Popline and African Index Medicus were searched up to 6th July 2011 using search terms for HIV, pregnancy and the following direct obstetric complications: obstetric haemorrhage, pregnancy-induced hypertension, dystocia and intrauterine infections (see Appendix A for the full search strategy). There were no language or publication date restrictions. All abstracts were reviewed by a single author (CC) and a 20% sample of abstracts was independently reviewed by a second researcher. Full text copies of potentially relevant papers were obtained and the reference lists of review articles and articles which were included in this systematic review were searched for further relevant publications.

Eligibility Criteria

Studies were eligible for inclusion if they compared the occurrence of direct obstetric complications during pregnancy, delivery and/or up to 365 days postpartum between HIV-infected and uninfected women using a cohort, cross-sectional or case-control design. Obstetric complications relevant for this review were categorised as: obstetric haemorrhage (including placenta praevia, placental abruption, antepartum haemorrhage, peri- or postpartum haemorrhage and retained placenta); pregnancy-induced hypertension (including eclampsia and pre-eclampsia); dystocia (including prolonged or obstructed labour, abnormal presentation and uterine rupture); and intrauterine infections (including puerperal sepsis, wound infection and endometritis). Studies were required to have a sample size of at least 30 women in each study group with no restrictions on country, dates or whether the study was population or facility-based.

Data Extraction and management

Data were extracted by a single author (CC) on: study location, dates, design and population, definition and ascertainment of the obstetrical outcome (e.g. whether haemorrhage was ascertained through visual estimate or actual measurement of blood loss), the mode of delivery, 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 women with the obstetric complication by HIV status, the type of denominator (pregnancy, live births or women) and the denominator.

Study populations described in more than one paper were included only once, using data from the paper with the most detailed information. When more than one obstetrical

outcome was evaluated in a single study, these were extracted and treated as separate data sets.

Assessment of risk of bias

The risk of bias for each data set was assessed using the component approach adopted by The Cochrane Collaboration.(86) All data sets were assessed on the definition and ascertainment of the obstetric complication, the completeness of data, adjustment for confounding and selection of the comparison group. Each of the quality criteria were classified as having a low risk or high risk of bias for each data set. For example, a data set was classified as having a high risk of bias for outcome ascertainment if methods which were likely to lead to cases being missed were used (e.g. hospital record review). Where there was insufficient information to assess the risk of bias, the data set was classified as at an unclear risk of generating bias.

Statistical Methods

All analyses were carried out using STATA 12.0. The association between HIV and each obstetric complication was estimated using odds ratios (OR). Summary measures of effect for each obstetric complication were obtained by conducting a random-effects meta-analysis of the best effect estimate available from each study. Where an adjusted OR was available from the paper, this was taken as the best estimate; otherwise the crude estimate was used. Articles do not generally state whether there is overlap between categories of obstetric complications, for example, whether the women who have puerperal sepsis are also the women who are included as having endometritis. We therefore only provide summary estimates for sub-categories within each broad obstetric grouping. As the effect of HIV on the obstetric complications may vary by the mode of delivery, studies which included either vaginal deliveries only or both vaginal and caesarean deliveries were considered separately from studies which only included caesareans. Publication bias was assessed using funnel plots and was formally tested using Begg's test.(132)

Additionally, for data sets which included vaginal and caesarean section deliveries, a meta-analysis was conducted to assess whether HIV-infected women had increased odds of caesarean. ORs were computed for each study rather than each data set.

4.2.4 Results

Search Strategy Results

We initially identified 18,949 titles and abstracts and 1,291 of these were retained for full text review (Figure 4.1). Of the 1,291 articles, 1,247 were excluded as they did not contain relevant data. A total of 44 studies, providing 66 data sets, were included. Seventeen data sets contained information on obstetric haemorrhage (one caesarean only study), 19 on hypertensive disorders of pregnancy (one caesarean only study), five on dystocia and 25 data sets contained information on intrauterine infections (12 caesarean only studies and one study which was stratified by mode of delivery and therefore provided two data sets).

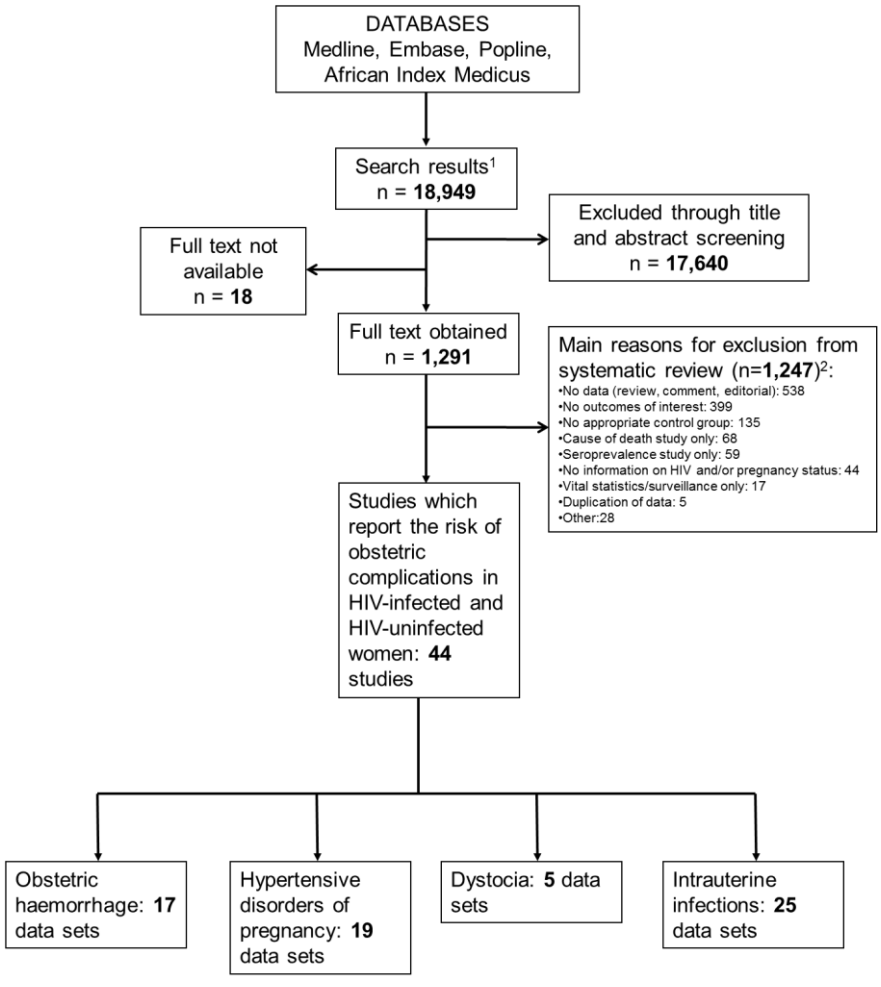

Figure 4.1: Flow chart of study selection for inclusion in the systematic review
[1]After removal of duplicates
[2]Articles may have been excluded for multiple reasons

Study Characteristics

Table 4.1 (page 86) describes the 51 eligible data sets based on vaginal deliveries or all modes of delivery. The 15 data sets which only included women undergoing a caesarean section are described in Table 4.2 (page 103). Overall, study populations were from Spain,(65, 133, 134) France,(61) the UK,(135) Germany,(136) Holland,(137) Italy,(66) the USA,(60, 118, 119, 138-141) Mexico,(120) Dominican Republic,(142) Brazil,(100, 143) Kenya,(115, 144-146), Ethiopia,(147) Rwanda,(59, 111) Uganda,(112, 148, 149) Nigeria,(150-152) Zimbabwe,(153) South Africa,(63, 64, 103, 154, 155) India,(117, 156) and Thailand.(157, 158) One study was conducted in Italy, Spain, Sweden, Poland and Ukraine(159) and another was conducted in Malawi, Tanzania and Zambia.(160) All studies were conducted in health facilities. Thirty-four of the data sets (52%) were conducted when ART was available in the study population.

Risk of Bias Within and Between Data Sets

The assessment of the risk of bias is summarised in Table 4.3 (page 108) and Table 4.4 (page 115). Only 23 of the 66 data sets provided a definition for the obstetric complication: from eight of the 19 data sets (42%) reporting on hypertensive disorders to seven amongst the 25 data sets (28%) for intrauterine infections. The risk of bias in the ascertainment of obstetric complications cases was judged to be high for 29 of the 66 data sets; most of which relied on medical records to ascertain the nature of the complication.

Very few studies had sufficient information on the completeness of the data to enable the risk of bias to be assessed and only 17 of 66 data sets were classified as at low risk of bias. In particular, studies relying on medical records tended not to report how many records had to be excluded due to missing information (e.g. HIV status).

Overall, 25 of 66 data sets either adjusted for confounders in their analysis or matched the HIV-infected and uninfected women with respect to some key confounders. The majority of the data sets (58 of 66) were judged to be at low risk of bias in the selection of the comparison group of HIV-uninfected women.

There was no evidence of publication bias for any of the outcomes included in the analysis with the exception of pre-eclampsia (p=0.01) (Figure 4.2).

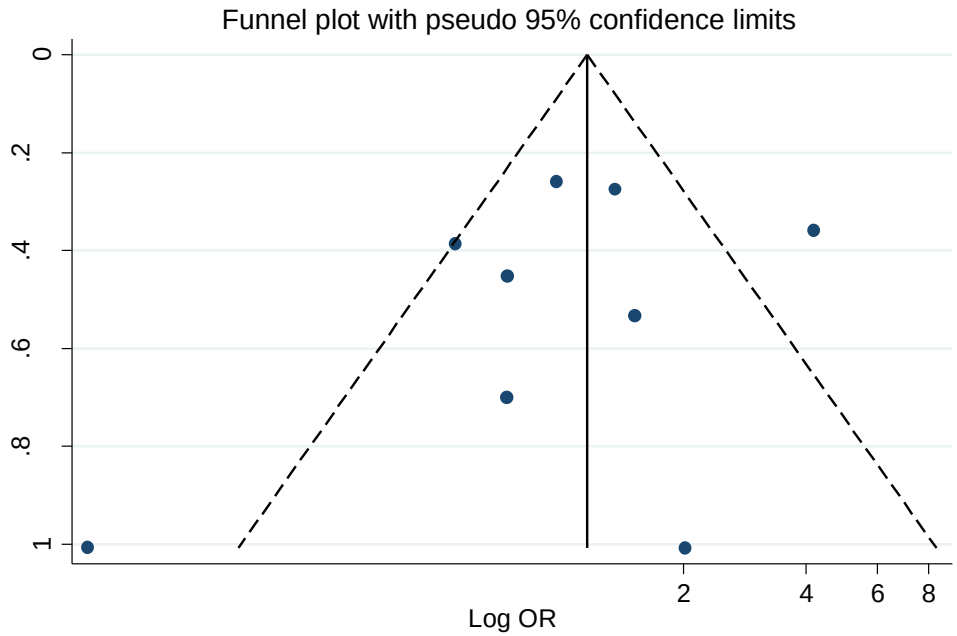

Figure 4.2: Funnel plot for studies measuring the association between HIV and pre-eclampsia

Effect of HIV on Obstetric Haemorrhage

The prevalence of antepartum haemorrhage was higher in HIV-infected than uninfected women in four out of five data sets (Table 3.1). Meta-analysis indicated that HIV-infected women have double the odds of antepartum haemorrhage [summary odds ratio (OR): 2.06, 95% confidence interval (CI): 1.42-2.97] (Figure 4.3). There was no evidence for between-study heterogeneity (I^2: 27.5%, p-value=0.24). Based on three data sets, there was no evidence for an association between HIV and either placenta praevia (summary OR: 1.02, 95% CI: 0.33-3.14, I^2: 0%, p-value=0.70) or placental abruption (summary OR: 1.61, 95% CI: 0.12-20.79, I^2: 76.1%, p-value=0.02) (Figure 4.3).

Thirteen data sets compared the prevalence of postpartum haemorrhage in HIV-infected and uninfected women with ORs ranging from 0.25 to 11.18. The meta-analysis suggests there is no evidence that HIV increases the odds of postpartum haemorrhage (summary OR: 1.28, 95% CI: 0.69-2.38, I^2: 53.4%, p=0.01). Similarly, there was no evidence for increased odds of retained placenta with HIV infection (summary OR: 1.28, 95% CI: 0.80-2.06, I^2: 0%, p=0.50).

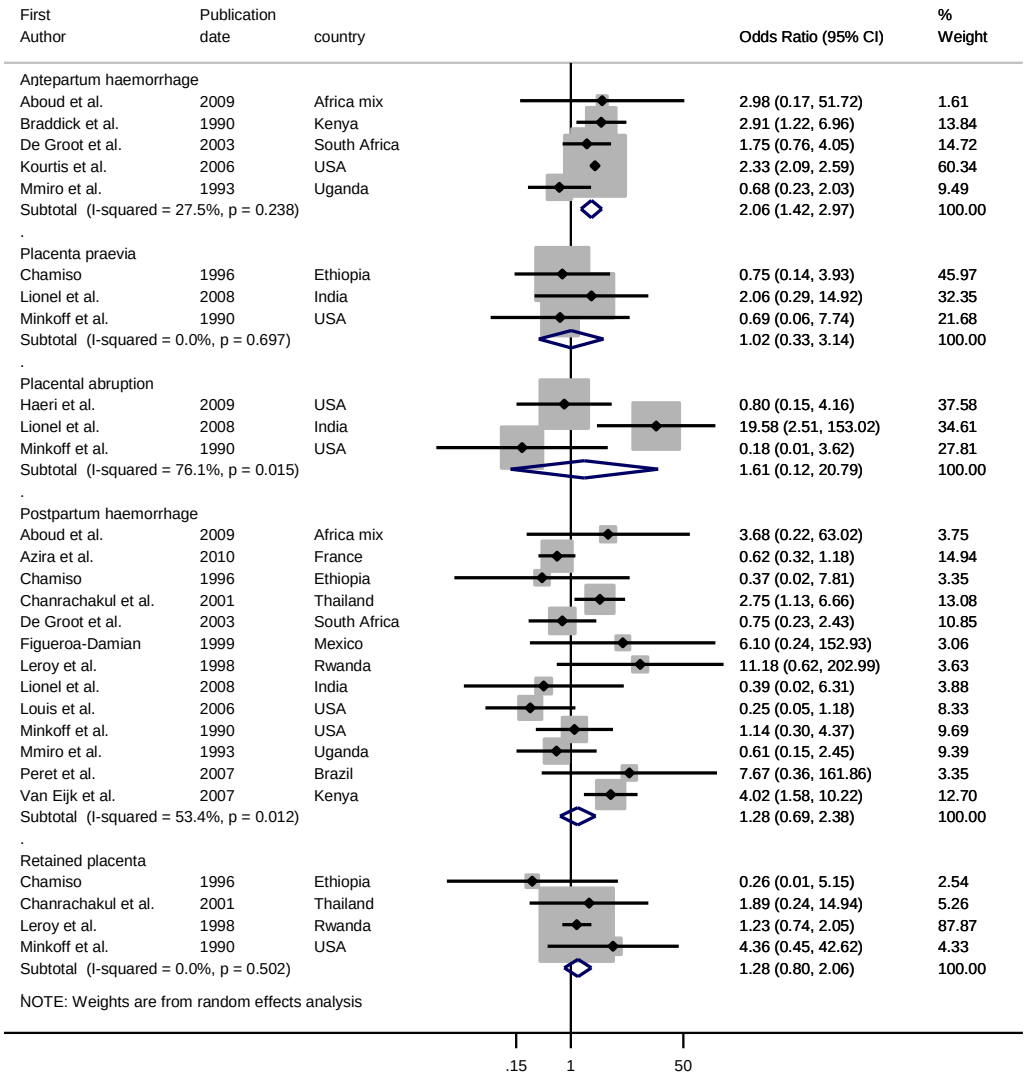

Figure 4.3: Forest plot showing the strength of association between HIV and maternal haemorrhage

One study looked at the association between HIV and postpartum haemorrhage amongst women undergoing a caesarean section (Table 3.2). There was no evidence of an association between HIV and postpartum haemorrhage (OR: 0.44, 95%CI: 0.19-1.04).

Effect of HIV on Hypertensive Disorders of Pregnancy

Out of the 11 data sets with data on pregnancy-induced hypertension, eight found that HIV-infected women were at increased risk of pregnancy-induced hypertension (Table 3.1). The meta-analysis showed some evidence for increased odds of pregnancy-induced hypertension with HIV infection (summary OR: 1.46, 95% CI: 1.03-2.05). However, there was strong evidence for between-study heterogeneity (I^2: 79.3%, p-value<0.001) (Figure 4.4).

Nine data sets examined the association between HIV and pre-eclampsia; four of these found a higher prevalence in HIV-infected women than uninfected women. There was no evidence that HIV infection was associated with pre-eclampsia (summary OR: 1.04, 95% CI: 0.60-1.79, I^2: 70.5%, p-value=0.001).

The ORs from the four data sets comparing the prevalence of eclampsia in HIV-infected and uninfected women varied from 0.39 to 38.47. The meta-analysis produced a summary OR of 2.56, however the confidence intervals were very wide (95% CI: 0.15-44.11) and there was strong evidence for between-study heterogeneity (I^2: 96.6%, p-value<0.001).

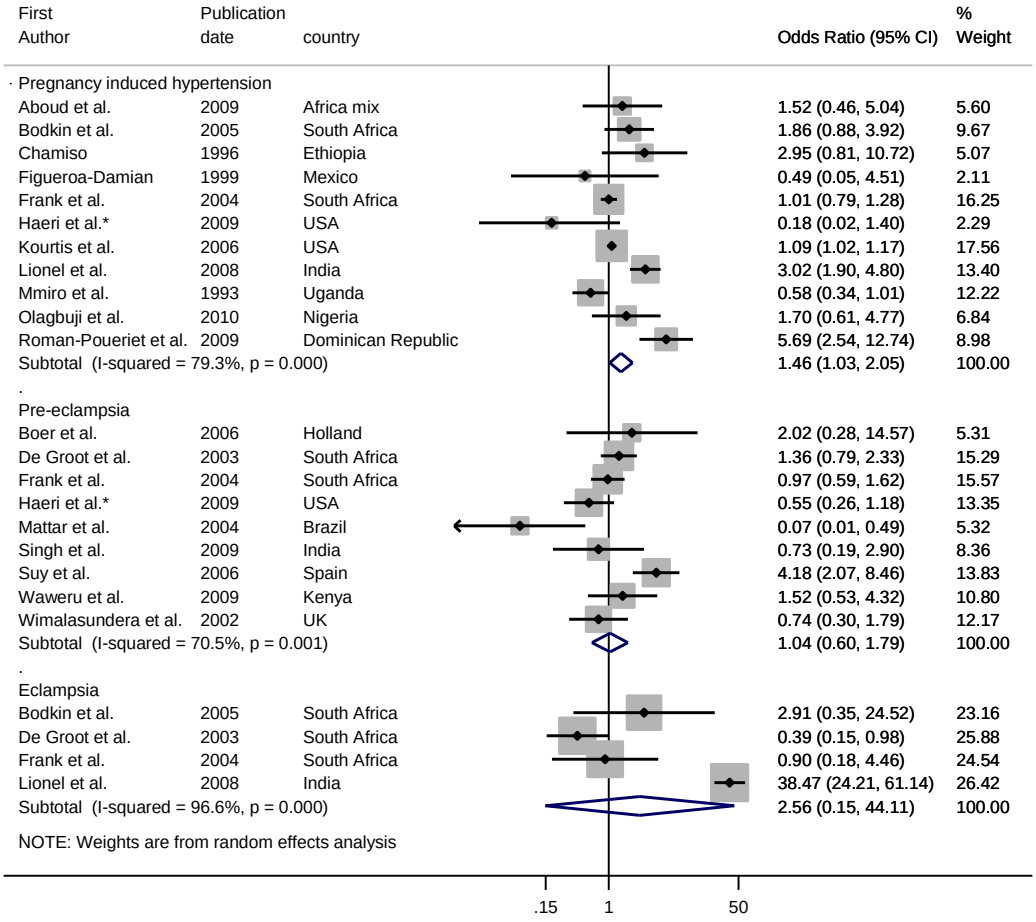

Figure 4.4: Forest plot showing the strength of association between HIV and hypertensive disorders of pregnancy
***Adjusted estimate**

There was one data set from Nigeria which was restricted to caesarean sections (Table 3.2). There was no evidence of an association between HIV and postpartum pregnancy-induced hypertension (OR: 0.33, 95% CI: 0.01-8.21).

Effect of HIV on Dystocia

There were only six data sets where the outcome could be broadly categorised as dystocia (Table 3.1, Figure 4.5). One data set from Rwanda found no association between HIV and dystocia (OR: 1.04, 95% CI 0.59-1.82), whilst a study from Thailand indicated that HIV-infected women have nearly eight times the odds of prolonged labour compared with uninfected women (OR: 7.86, 95% CI: 4.64-13.33). Two data sets reported on abnormal presentation, and there was no evidence for an association between HIV and abnormal presentation in the meta-analysis (summary OR: 1.17, 95% CI: 0.68-2.03, I^2: 0%, p=0.50). Conversely, both data sets which compared the prevalence of uterine rupture showed an increased risk in HIV-infected women, giving a summary OR of 3.14 (95% CI: 1.51-6.50, I^2:0%, p=0.89).

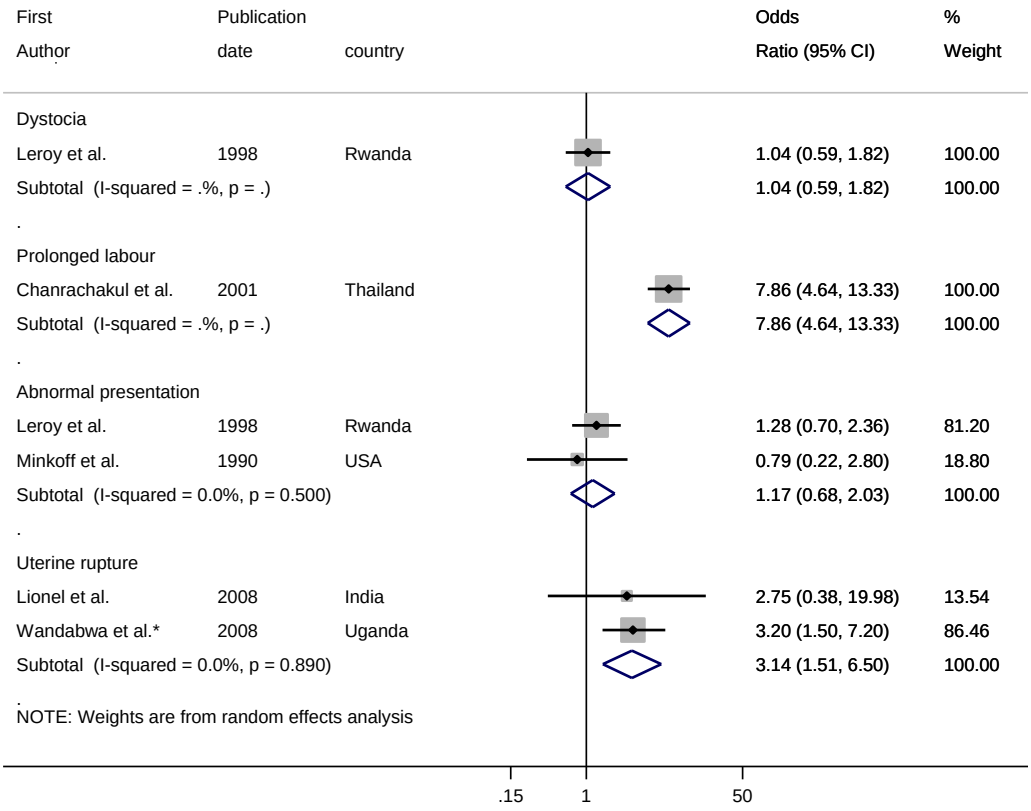

Figure 4.5: Forest plot showing the strength of association between HIV and dystocia
***Adjusted estimate**

Effect of HIV on Intrauterine Infections

Figure 4.6 shows the association between HIV and intrauterine infections. Meta-analysis based on four data sets indicated that HIV-infected women have over three times the odds of having puerperal sepsis compared with uninfected women (summary OR: 3.43, 95% CI: 2.00-5.85, I^2: 9.4%, p-value=0.35). There was also evidence from eight data sets that HIV-infected women had over 2.5 times the risk of endometritis compared with uninfected women (summary OR: 2.51, 95% CI: 1.50-4.21, I^2: 19.6%, p-value=0.27).

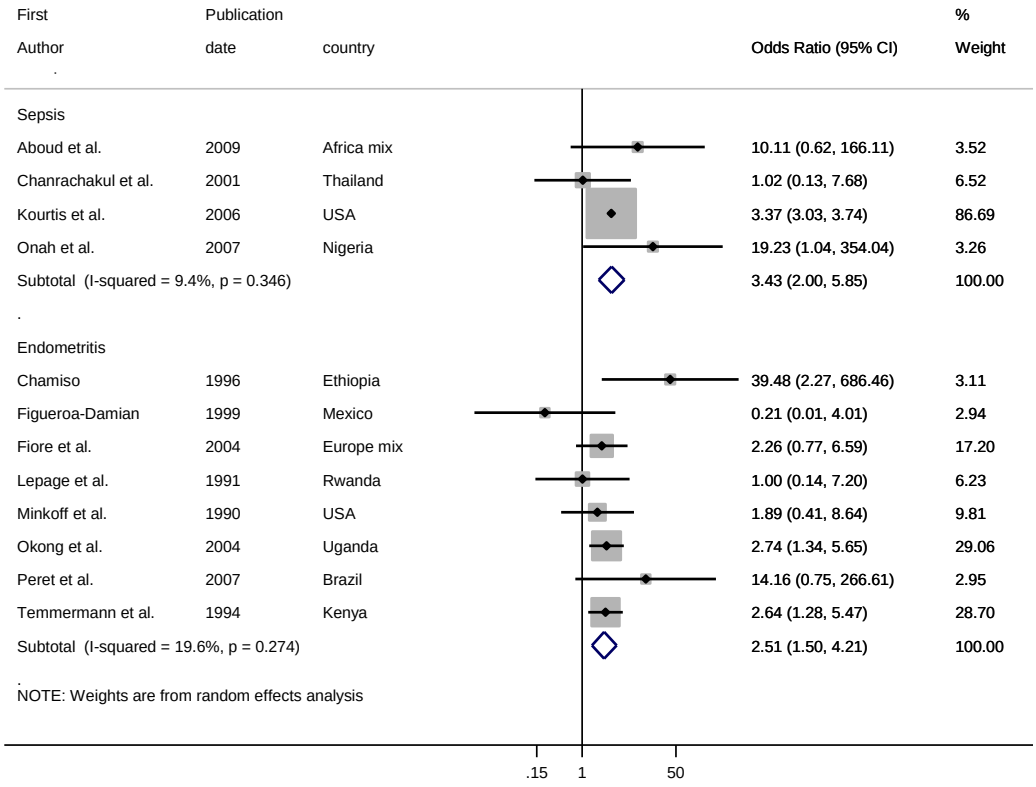

Figure 4.6: Forest plot showing the strength of association between HIV and intrauterine infections amongst studies which included vaginal deliveries

The results of the meta-analyses for women who had a caesarean section are presented in Figure 4.7. The pooled OR from four data sets indicated that HIV-infected women had nearly six times higher odds of suffering from puerperal sepsis compared with their uninfected counterparts (summary OR: 5.81, 95% CI: 2.42-13.97, I^2: 0%, p-value=0.93). Amongst the ten data sets which contained information on wound infection, the pooled OR was 1.75 (95% CI: 1.20-2.55) although there was weak evidence for between-study heterogeneity (I^2: 30.1%, p=0.17). Finally, there were 12 studies which looked at endometritis in HIV-infected and uninfected women; nine found a higher occurrence in HIV-infected women. The meta-analysis showed that HIV-infected women had over double the odds of endometritis than uninfected women (OR:

1.86, 95% CI: 1.28-2.71). There was good evidence for between-study heterogeneity (I^2: 47.0%, p=0.04).

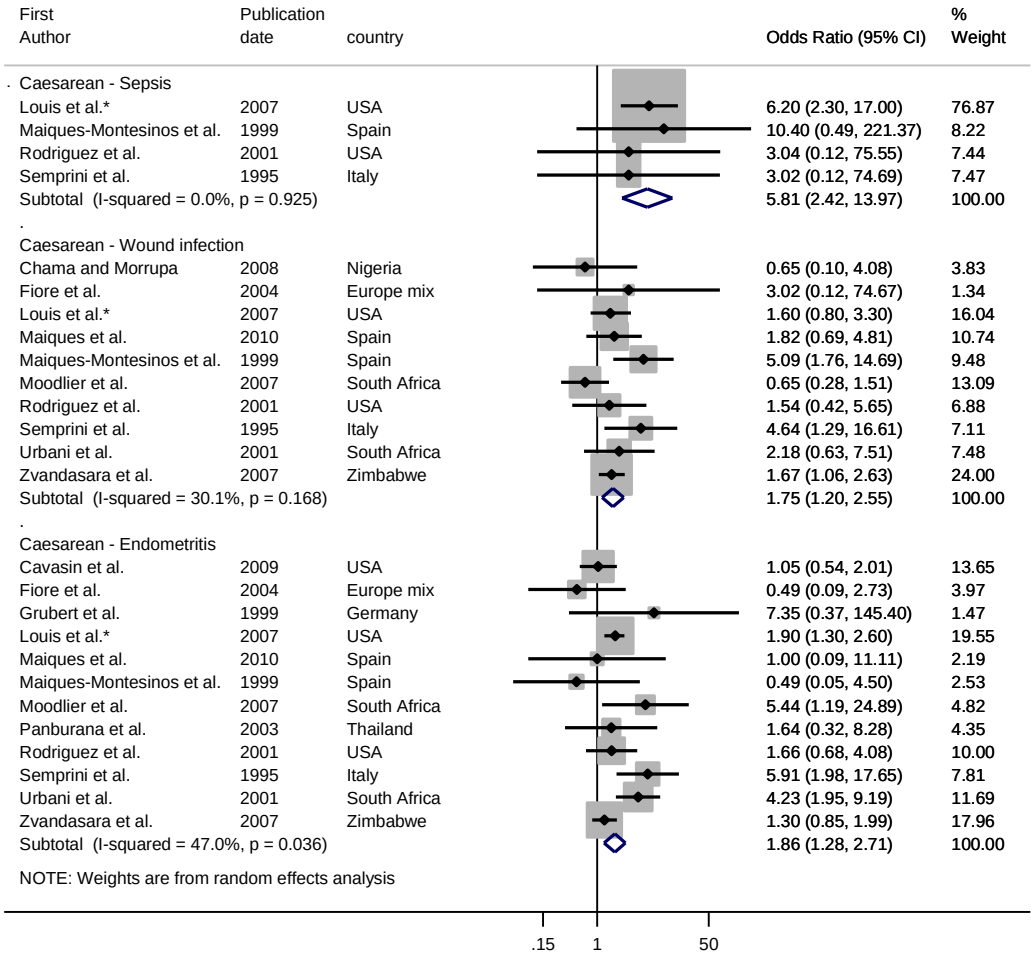

Figure 4.7: Forest plot showing the strength of association between HIV and intrauterine infections amongst studies which only included caesarean deliveries
***Adjusted estimate**

Caesarean Section

Of the studies which included vaginal and caesarean section deliveries, 13 did not provide information on the proportion of HIV-infected and uninfected women who had a caesarean (one stated that there was no difference in the mode of delivery in HIV-infected and uninfected women, one was restricted to only vaginal deliveries, three only followed women during pregnancy and eight did not provide any information on the proportion of infected and uninfected women having caesareans). Figure 4.8 shows the relative odds of having a caesarean for HIV-infected compared with uninfected women across the 19 studies which provided data. The ORs varied from 0.40 to 5.55 and there was no evidence that HIV-infected women were more likely to have a caesarean compared with uninfected women [summary OR: 1.20, 95% CI: 0.81-1.78]. However, there was strong evidence for between-study heterogeneity (I^2: 88.4%, p<0.001).

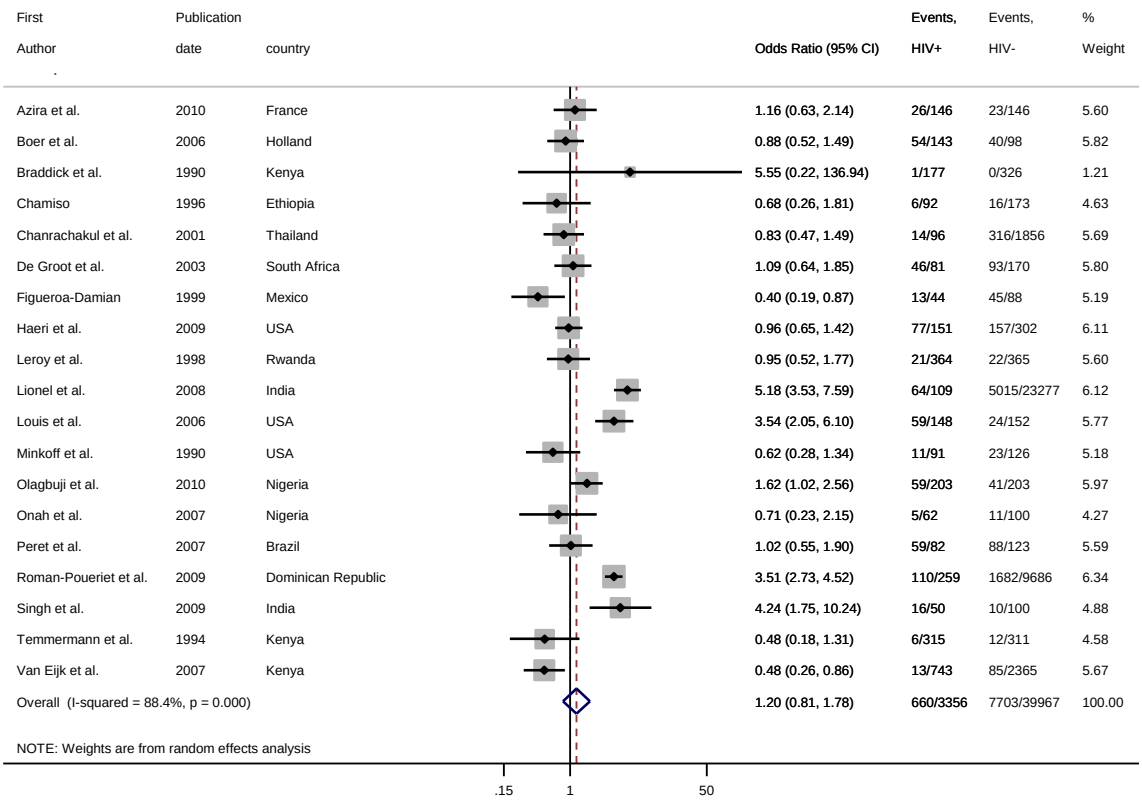

Figure 4.8: Forest plot showing the strength of association between HIV and odds of having a caesarean

4.2.5 Discussion

Our systematic review suggests that HIV increases the risk of intrauterine infections during pregnancy, delivery or the postpartum. Studies including vaginal and caesarean deliveries indicated that HIV-infected women had over three times the risk of a puerperal sepsis compared with uninfected women; this figure increased to nearly six amongst studies only including women who delivered by caesarean. The evidence for an association between HIV and other direct obstetric complications was inconsistent. Whilst HIV was associated with an increased risk of antepartum haemorrhage, there was no evidence of an increased risk of placenta praevia, placental abruption, postpartum haemorrhage or retained placenta. Similarly, HIV did appear to increase the risk of pregnancy-induced hypertension, but not of pre-eclampsia and eclampsia. Finally, we found an association between HIV and both uterine rupture and prolonged labour, but not between HIV and other complications of dystocia.

The higher risk of intrauterine infections in HIV-infected women is biologically plausible, as the immune suppression associated with HIV increases susceptibility to infection.(161) Caesarean sections may increase the risk of postpartum infection, but

caesarean sections were equally common in HIV-infected and uninfected women, and the excess risk of intrauterine infections in HIV-infected women persisted among caesarean only deliveries. Whether the excess risk of endometritis and puerperal sepsis in the intra- and postpartum period is directly attributable to the pregnancy or indirectly related to HIV or AIDS-associated infections is uncertain. Intrauterine infections were mostly ascertained from hospital records, definitions were lacking, it was not always clear whether the infection was diagnosed during pregnancy or the postpartum and microbiological examination was not done. The signs and symptoms suggestive of endometritis and puerperal sepsis in intra- or postpartum women may have been a direct consequence of the increased prevalence of sexually transmitted infections associated with HIV.(162, 163) In the 2008-2010 confidential enquiries into maternal deaths in South Africa, only 6% of maternal deaths in HIV-infected women were attributed to pregnancy-related sepsis, while 62% of deaths were attributed to non-pregnancy-related infections.(164) Without clear definitions misclassification of non-pregnancy-related infections as pregnancy-related, or vice versa, cannot be excluded.

We did not find a consistent association between HIV and the risk of either haemorrhage, dystocia or hypertensive diseases of pregnancy. HIV-related thrombocytopenia affects around 10% of HIV-infected individuals and 30% of individuals with AIDS,(165-167) but it rarely leads to severe bleeding.(165, 167) The association between HIV and uterine rupture, concomitant with no association between HIV and other categories of dystocia, may suggest that delayed care seeking in HIV-infected women plays a role. However, this finding was based on two studies only, and caution is required in its interpretation. The observed associations between HIV and broadly defined categories of complications such as antepartum haemorrhage or hypertensive diseases – whereas no association was found between HIV and more narrowly defined clinical diagnoses such as placenta praevia, placental abruption, pre-eclampsia or eclampsia - suggests that measurement errors may have occurred. Unfortunately, few studies provided information on the number of women with more than one diagnosis, and we were not able to pool findings within the broad obstetric categories.

The lack of an association between HIV and caesarean section is surprising. Caesarean sections have been recommended to prevent the mother-to-child transmission (PMTCT) of HIV in many regions,(168, 169) and the most common indication for caesarean section in HIV-infected women in the studies reviewed was PMTCT of HIV (data not shown). It is possible that clinicians, particularly in low income

countries, weigh the health risks associated with caesarean sections against those of PMTCT, and are perhaps more cautious about performing caesarean sections in HIV-infected women. Although recent guidelines recommend that women with very low viral loads who are on ART do not need a caesarean for PMTCT of HIV (170) we would expect a higher rate of caesareans amongst HIV-infected women in high-income countries given the time period in which the studies were conducted. Stratifying the meta-analysis by high and low income countries did not alter the findings (data not shown). We did not systematically review the literature to assess the association between HIV and caesarean sections, however, and some studies may have been missed.

This review was comprehensive covering a long time period with no restriction on language, world region or type of study. The studies found were predominantly conducted in tertiary health facilities, however, resulting in the enrolment of a higher risk group of pregnant women. While this will lead to an overestimation in the frequency of obstetric complications, it is unlikely this will have affected the relative odds comparing HIV-infected and uninfected women. The main limitation of this review is the poor quality of included studies, none of which were classified as at low risk of bias across all the quality components. Notably, only 25 data sets controlled for key confounders, either through matching HIV-infected and uninfected women or through adjustment in the analysis. Furthermore, very few studies provided information on how the obstetric complications were defined or ascertained. Whether the risks and stigma associated with HIV may result in health professionals reporting complications differentially in HIV-infected and uninfected women is not known, but information bias certainly needs considering. Unfortunately, due to the limited number of studies included in this review, it was not possible to tease out the effect of ART by restricting analyses to studies conducted when ART was available.

HIV-infected women are thought to be eight times more likely to die in pregnancy or the postpartum than HIV-uninfected women,(98, 171) and the excess mortality attributable to HIV among HIV-infected women is about 994 per 100,000 pregnant women.(98) While the increased risk of puerperal sepsis and endometritis in HIV-infected women contributes to this, direct obstetric causes only explain a tiny fraction of the excess mortality. Studies on the causes of death in pregnant or postpartum women by HIV status are scarce, except for the South African confidential enquiries, the most recent of which cover 2,756 and 1,149 maternal deaths in HIV-infected and uninfected women respectively.(164) The 2008-2010 confidential enquiries suggest that most deaths in HIV-infected pregnant and postpartum women are due to non-pregnancy-related

infections, including pneumonia, tuberculosis and meningitis.(164) Although anaemia is thought to be exacerbated by HIV,(131) the confidential enquiries find a similar proportion of maternal deaths attributable to severe anaemia in HIV-infected and uninfected women (8% and 10% respectively).(164)

It is essential to ensure that both HIV-infected and uninfected pregnant woman have ready access to high quality antenatal and delivery services to correctly diagnose and manage direct obstetric complications when they occur. HIV-infected pregnant women will also benefit from prophylactic antibiotics during labour to reduce their risk of intrauterine infections.(172) However, given that most of the excess mortality associated with HIV in pregnancy is directly related to HIV rather than to a higher risk of obstetric complications, the greatest impact on pregnancy-related mortality will come from ensuring that HIV-infected pregnant women have adequate access to ART.(173) The World Health Organization recommends the provision of lifelong ART treatment for all HIV-infected pregnant women with a CD4 count below 350 cells/mm^3, but many countries are still transitioning to these guidelines.(174, 175) Scaling up Option B+, where all pregnant mothers start ART regardless of their CD4 cell count and then continue taking it for life, has been proposed as an additional strategy to benefit maternal health; however, any benefit must be carefully measured against the potential pitfalls which include the high financial costs of such a programme and possible poor adherence to ART amongst women who perceive themselves to be healthy.(176)

Table 4.1: Summary of studies of HIV and obstetric complications which included births by vaginal delivery

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Haemorrhage										
Aboud *et al.* 2009(160)	Prospective Cohort [from a randomised controlled trial (RCT)]	Multiple hospitals and antenatal clinics in Malawi (Blantyre and Lilongwe) and Zambia (Lusaka) (2001-2003)	All HIV+ women enrolled and one HIV- woman enrolled for every five HIV+ women.	No information provided	No	Antepartum haemorrhage (no further details)	0.5 *(1,558)*	0 *(271)*	2.98 (0.17-51.72)	-
						Postpartum haemorrhage (no further details)	0.6 *(1,558)*	0 *(271)*	3.68 (0.22-63.02)	-
Azira *et al.*, 2010(61)	Retrospective Cohort	One maternity hospital in Paris, France (2001-2006)	All HIV+ women with an undetectable viral load at 36 weeks gestation and one HIV- control for each HIV+ woman matched for parity, previous c-section and geographic origin. Excluded deliveries before 37th week of gestation, multiple pregnancies, non cephalic presentation or elective c-section and for HIV+ women viral load had to be undetectable.	**HIV+**: 17.8% had a c-section **HIV-**: 15.7% had a c-section	Yes	Postpartum haemorrhage defined as blood loss≥500mL after delivery	12.3 *(146)*	18.5 *(146)*	0.62 (0.32-1.18)	-
Braddick *et al.*, 1990(144)	Prospective Cohort	One maternity hospital in Nairobi, Kenya (1986-1989)	All HIV+ women and HIV- women who lived close to the follow-up clinic.	**HIV+**: 0.5% had a c-section **HIV-**: No c-sections	No	Antepartum haemorrhage defined as bleeding during the third trimester	8.1 *(161)*	2.9 *(307)*	2.91 (1.22-6.96)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Chamiso, 1996(147)	Prospective Cohort	One maternity hospital in Addis Ababa, Ethiopia (1993-1995)	All HIV+ women and HIV- women matched to the HIV+ women for age and parity.	**HIV+**: 6.5% had a c-section **HIV-**: 9.2% had a c-section	No	Placenta praevia (no further details)	2.2 *(92)*	2.9 *(173)*	0.75 (0.14-3.93)	-
						Postpartum haemorrhage (no further details)	0 *(92)*	1.2*(173)*	0.37 (0.02-7.81)	-
						Retained placenta (no further details)	*0 (92)*	1.7 *(173)*	0.26 (0.01-5.15)	-
Chanrachakul *et al.*, 2001(157)	Retrospective Cohort	One tertiary hospital in Bangkok, Thailand (1991-1999)	All nulliparous HIV+ women delivering from 1991-1999 and all non-private, nulliparous HIV- women admitted in 1998. Excluded emergency c-section, deliveries before 37th week of gestation, multiple pregnancies or non cephalic presentation.	**HIV+**: 14.6% had a c-section **HIV-**: 15.0% had a c-section; analysis restricted to vaginal deliveries	No[1]	Postpartum haemorrhage (no further details)	7.3 *(82)*	2.8 *(1,540)*	2.75 (1.13-6.66)	-
						Retained placenta (no further details)	1.2 *(82)*	0.7 *(1,540)*	1.89 (0.24-14.94)	-
De Groot *et al.*, 2003(103)	Retrospective Cohort	One high risk obstetric unit in Bloemfontein, South Africa (2001)	All HIV+ women and two HIV- controls for every HIV+ woman enrolled.	**HIV+**: 56.8% had a c-section **HIV-**: 55.7% had a c-section	No[1]	Antepartum haemorrhage defined as any bleeding occurring during pregnancy but before delivery	13.6 *(81)*	8.2 *(170)*	1.75 (0.76-4.05)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
						Postpartum haemorrhage defined as a fall in Hb level≥3g/dL associated with vaginal bleeding	4.9 *(81)*	6.5 *(170)*	0.75 (0.23-2.43)	-
Figueroa-Damian, 1999(120)	Prospective Cohort	Institute of Perinatology in Mexico City, Mexico (1989-1997)	44 HIV+ women and two HIV- controls for each HIV+ woman, matched on age and socioeconomic status.	**HIV+**: 29.9% had a c-section **HIV-**: 51.2% had a c-section	Yes	Postpartum haemorrhage (no further details)	2-.3 *(44)*	0 *(88)*	6.10 (0.24-152.93)	-
Haeri *et al.*, 2009(138)	Retrospective Cohort	Two tertiary care centres in Columbia and North Carolina, USA (2000-2007)	All HIV+ women on ART and two HIV- controls for each HIV+ woman matched for age, race, parity, care location, delivery mode, insurance type and year of delivery. Excluded deliveries before 20 weeks gestation.	**HIV+**: 51.0% had a c-section **HIV-**: 52.0% had a c-section	Yes	Placental Abruption (no further details)	1.3 *(151)*	1.7 *(302)*	0.80 (0.15-4.16)	-
Kourtis *et al.*, 2006(118)	Retrospective Cohort	20% of all community hospitals in the USA (1994 & 2003)	All HIV+ and HIV- pregnant women between 15-44 years of age who were hospitalised.	No information provided	Yes	Antepartum haemorrhage defined according to ICD-9 codes	2.8 *(12,378)*	1.2 *(8,784,767)*	2.33 (2.09-2.59)	-
Leroy *et al*., 1998(59)	Prospective Cohort	One tertiary hospital in Kigali, Rwanda (1992-1993)	All HIV+ women and one HIV- control for each HIV+ woman matched for age. Only included women resident in Kigali who attended antenatal clinic two days a week and wished to deliver in the hospital.	**HIV+**: 5.8% had a c-section **HIV-**: 6.0% had a c-section	No	Postpartum haemorrhage (no further details)	1.4 *(364)*	0 *(365)*	11.18 (0.62-202.99)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
						Retained placenta (no further details)	12.1 *(305)*	10.1 *(308)*	1.23 (0.74-2.05)	-
Lionel *et al*., 2008(117)	Retrospective Cohort	One hospital in Vellore, India (2000-2002)	All HIV+ and HIV- women.	**HIV+**: 58.7% had a c-section **HIV-**: 21.5% had a c-section	Yes	Major placenta praevia	0.9 (109)	0.5 *(23,277)*	2.06 (0.29-14.92)	-
						Placental abruption (Grade III)	0.9 (109)	0.1 *(23,277)*	19.58 (2.51-153.02)	-
						Postpartum haemorrhage (no further details)	0 *(109)*	1.2 *(23,277)*	0.39 (0.02-6.31)	-
Louis *et al*., 2006(139)	Retrospective Cohort	One tertiary hospital in Detroit, USA (2000-2005)	All HIV+ women and a random selection of HIV- women.	**HIV+**: 39.9% had a c-section **HIV-**: 15.8% had a c-section	Yes	Postpartum haemorrhage (no further details)	1.4 *(148)*	5.3 *(152)*	0.25 (0.05-1.18)	-
Minkoff *et al*., 1990(60)	Prospective Cohort	Four prenatal clinics in New York, USA (1985-1989)	All HIV+ women who had a live, singleton birth; in three of the prenatal clinics all HIV- women were also recruited, and in one of the clinics two HIV- controls were selected for each HIV+ woman.	**HIV+**: 12.0% had a c-section **HIV-**: 18.0% had a c-section	No	Placenta praevia (no further details)	1.2 *(85)*	1.7 *(118)*	0.69 (0.06-7.74)	-
						Placental abruption (no further details)	0 *(85)*	2.5 *(118)*	0.18 (0.01-3.62)	-
						Peripartum haemorrhage (no further details)	4.5 *(89)*	4.0 *(126)*	1.14 (0.30-4.37)	-
						Retained placenta (no further details)	3.4 *(89)*	0.8 *(126)*	4.36 (0.45-42.62)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Mmiro *et al*., 1993(112)	Prospective Cohort	One university hospital in Kampala, Uganda (1988-1990)	All HIV+ women and a random 10% sample of HIV- women. Only included women who lived within 15km of Mulago and agreed to deliver in the hospital.	No difference in the mode of delivery in HIV+ and HIV- women	No	Antepartum haemorrhage (no further details)	0.9 *(539)*	1.4 *(660)*	0.68 (0.23-2.03)	--
						Postpartum haemorrhage (no further details)	0.6 *(539)*	0.9 *(660)*	0.61 (0.15-2.45)	-
Peret *et al*., 1993(143)	Prospective Cohort	One maternity hospital in Belo Horizonte, Brazil (2001-2003)	82 HIV+ women and 123 HIV- women matched on mode of delivery, gestational age at delivery and maternal age. Only included women if they did not have chronic diseases and/or complications of pregnancy.	**HIV+**: 72.0% had a c-section **HIV-**: 72.0% had a c-section	Yes	Postpartum haemorrhage defined by clinical observation and/or need for at least one of the following interventions: uterotonic drugs, revision of the uterine cavity and the birth canal or curettage	2.4 *(82)*	0 *(123)*	7.67 (0.36-161.86)	-
Van Eijk *et al*., 2007(145)	Prospective Cohort	One large hospital in Kisumu, Kenya (1996-2000)	All women who delivered at the hospital if they had an uncomplicated singleton pregnancy at more than 32 weeks gestation, resided in Kisumu and had no underlying chronic illnesses.	**HIV+**: 3.1% had a c-section **HIV-**: 3.6% had a c-section	Not clear	Peripartum haemorrhage (no further details)	1.4 *(743)*	0.3 *(2,365)*	4.02 (1.58-2.33)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Hypertensive diseases of pregnancy										
Aboud *et al.* 2009(160)	Prospective Cohort (from an RCT)	Multiple hospitals and antenatal clinics in Malawi (Blantyre and Lilongwe) and Zambia (Lusaka) (2001-2003)	All HIV+ women enrolled and one HIV- woman enrolled for every five HIV+ women.	No information provided	No	Hypertension, with or without proteinuria, measured in the intrapartum period	1.7 *(1,558)*	1.1 *(271)*	1.52 (0.46-5.04)	-
Bodkin *et al.*, 2005(63)	Retrospective cohort	One tertiary hospital in Gautang, South Africa (2003)	A sample of HIV+ women selected using stratified random sampling (stratifying on normal risk, moderate risk or high risk pregnancy) and one HIV- control selected for every two HIV+ women.	Only follows up women in ante-partum period	Yes	Pregnancy-induced hypertension (no further details)	17.0 *(212)*	9.9 *(101)*	1.86 (0.88-3.92)	-
						Eclampsia (no further details)	2.8 *(212)*	1.0 *(101)*	2.91 (0.35-24.52)	-
Boer *et al.*, 2006(137)	Retrospective cohort	Two medical centres in Amsterdam and Rotterdam, Holland (1997-2003)	All HIV+ treated with ART and two HIV- controls for each HIV+ woman matched on maternal age, parity, ethnicity, and being singleton or twin. The controls had to be healthy and not referred, not have had obstetric complications in the past and live near the hospital.	**HIV+**: 40.8% had a c-section **HIV-**: 12.8% had a c-section	Yes	Pre-eclampsia (during pregnancy until seven days postpartum) defined according to the definition of the International Society for the Studies of Hypertension in Pregnancy	2.0 *(98)*	1.0 *(196)*	2.02 (0.28-14.57)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Chamiso, 1996(147)	Prospective Cohort	One maternity hospital in Addis Ababa, Ethiopia (1993-1995)	All HIV+ women and HIV- women matched to the HIV+ women for age and parity.	**HIV+**: 6.5% had a c-section **HIV-**: 9.2% had a c-section	No	Pregnancy-induced hypertension defined as an increment in systolic blood pressure of 30 mmHg and in diastolic blood pressure of 15 mmHg from the pre- or early pregnancy level of blood pressure	6.5 *(92)*	2.3 *(173)*	2.95 (0.81-10.72)	-
De Groot *et al.*, 2003(103)	Retrospective Cohort	One high risk obstetric unit in Bloemfontein, South Africa (2001)	All HIV+ women and two HIV- controls for every HIV+ woman enrolled.	**HIV+**: 56.8% had a c-section **HIV-**: 55.7% had a c-section	No[1]	Pre-eclampsia defined as systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥ 90 mmHg, on at least 2 occasions 4 hours or more apart and proteinuria of ≥ 0.3 g/24 hours)	43.2 *(81)*	35.9 *(170)*	1.36 (0.79-2.33)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
						Eclampsia defined as 1+ convulsions which could not be explained by other cerebral conditions, in a patient with pre-eclampsia	7.4 *(81)*	17.1 *(170)*	0.39 (0.15-0.98)	-
Figueroa-Damian, 1999(120)	Prospective Cohort	Institute of Perinatology in Mexico City, Mexico (1989-1997)	44 HIV+ women and two HIV- controls for each HIV+ woman, matched on age and socioeconomic status.	**HIV+**: 29.9% had a c-section **HIV-**: 51.2% had a c-section	Yes	Acute hypertensive disorder of pregnancy (no further details)	2.3 *(44)*	4.6 *(88)*	0.49 (0.05-4.51)	-
Frank *et al.*, 2004(64)	Retrospective Cohort	One tertiary hospital and five primary care clinics in Johannesburg, South Africa (2002)	Random sample of HIV+ and HIV- pregnant Soweto residents who delivered at a gestational age of 20 weeks or more in a public health facility.	No information provided	No	Pregnancy-induced hypertension which includes proteinuric hypertension, gestational hypertension, non proteinuric hypertension and chronic hypertension	14.9 *(704)*	14.8 *(1,896)*	1.01 (0.79-1.28)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
						Pre-eclampsia defined as hypertension (diastolic blood pressure of ≥ 90 mm Hg on 2+ occasions, 4 hours apart) associated with proteinuria which developed after 20 weeks of pregnancy	2.1 *(704)*	3.0 *(1,896)*	0.97 (0.59-1.62)	-
						Eclampsia (no further details)	0.3 *(704)*	0.3 *(1,896)*	0.90 (0.18-4.46)	-
Haeri *et al.*, 2009(138)	Retrospective Cohort	Two tertiary care centres in Columbia and North Carolina, USA (2000-2007)	All HIV+ women on ART and two HIV- controls for each HIV+ woman matched for age, race, parity, care location, delivery mode, insurance type and year of delivery. Excluded deliveries before 20 weeks gestation.	**HIV+**: 51.0% had a c-section **HIV-**: 52.0% had a c-section	Yes	Gestational hypertension (no further details)	0.7 *(151)*	4.3 *(302)*	0.15 (0.02-1.14)	0.18 (0.02-1.40) [2]
						Pre-eclampsia defined according to the national working group for Hypertension in Pregnancy Guidelines	6.0 *(151)*	11.9 *(302)*	0.50 (0.25-1.01)	0.55 (0.26-1.18) [2]

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Kourtis *et al.*, 2006(118)	Retrospective Cohort	20% of all community hospitals in the USA (1994 & 2003)	All HIV+ and HIV- pregnant women between 15-44 years of age who were hospitalised.	No information provided	Yes	Pre-eclampsia /hypertensive disorders of pregnancy defined according to ICD-9 codes	7.7 *(12,378)*	7.1 *(8,784,767)*	1.09 (1.02-1.17)	-
Lionel *et al.*, 2008(117)	Retrospective Cohort	One hospital in Vellore, India (2000-2002)	All HIV+ and HIV- women.	**HIV+**: 58.7% had a c-section **HIV-**: 21.5% had a c-section	Yes	Pregnancy-induced hypertension (no further details)	21.1 *(109)*	8.1 *(23,277)*	3.02 (1.90-4.80)	-
						Eclampsia (includes antepartum, intrapartum and postpartum)	23.9 *(109)*	0.8 *(23,277)*	38.47 (24.21-61.14)	-
Mattar *et al.*, 2004(100)	Retrospective Cohort	One obstetric outpatient clinic in Sao Paulo, Brazil (2000-2002)	All women referred to the outpatient obstetric unit. Excluded women with pre-existing hypertension.	No information provided	Yes	Pre-eclampsia defined as hypertension (>=140 mmHg x 90 mmHg) and proteinuria (>=300 mg/24h) after 20 weeks of pregnancy	0.8 *(123)*	10.7 *(1,708)*	0.07 (0.01-0.49)	-
Mmiro *et al.*, 1993(112)	Prospective Cohort	One university hospital in Kampala, Uganda (1988-1990)	All HIV+ women and a random 10% sample of HIV- women. Only included women who lived within 15km of Mulago and agreed to deliver in the hospital.	No difference in the mode of delivery in HIV+ and HIV- women	No	Hypertension defined as diastolic blood pressure >90 mmHg	3.7 *(539)*	6.2 *(660)*	0.58 (0.34-1.01)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Olagbuji *et al*., 2010(150)	Prospective Cohort	One tertiary hospital in Benin City, Nigeria (2007-2008)	HIV+ women who did not have AIDS, chronic medical disorders predating the pregnancy, multiple gestation or duration of ART intake of less than 8 weeks. A single HIV- control was selected for each HIV+ woman.	**HIV+**: 29.1% had a c-section **HIV-**: 20.2% had a c-section	Yes	Pregnancy-induced hypertension (no further details)	4.9 *(203)*	3.0 *(203)*	1.70 (0.61-4.77)	-
Roman-Poueriet *et al*., 2009(142)	Retrospective Cohort	All main obstetric facilities, a social security hospital and two private clinics in La Romana, Dominican Republic (2003-2006)	All HIV+ and HIV- women.	**HIV+**: 42.5% had a c-section **HIV-**: 17.4% had a c-section	Yes	Pregnancy-induced hypertension (no further details)	2.8 *(252)*	0.5 *(9,003)*	5.69 (2.54-12.74)	-
Singh *et al*., 2009(156)	Prospective Cohort	One hospital in Imphal, India (2006-2008)	50 HIV+ and 100 HIV- women who did not have medical or obstetric complications during pregnancy.	**HIV+**: 32.0% had a c-section **HIV-**: 10.0% had a c-section	Yes	Pre-eclamptic toxaemia (no further details)	6.0 *(50)*	8.0 *(100)*	0.73 (0.19-2.90)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Suy *et al.*, 2006(133)	Prospective Cohort	One referral centre in Barcelona, Spain (2001-2003)	All HIV+ and HIV- women delivering after at least 22 weeks of pregnancy.	No information provided	Yes	Pre-eclampsia defined as the new onset of hypertension with 2 readings ≥6 hours apart of more than 140 mmHg systolic during gestation, delivery or immediate postpartum period, plus a dipstick reading of at least 1+ for proteinuria (0.1 g/l) confirmed by > 300 mg/24 h urine collection after 22 weeks of pregnancy	11.0 *(82)*	2.9 *(8,768)*	4.18 (2.07-8.46)	-
Waweru *et al.*, 2009(146)	Prospective Cohort	One maternity hospital in Kenya, Nairobi (Study dates not provided)	57 HIV+ and HIV- women who were randomly selected.	Only follows up women in ante-partum period	Not clear	Pre-eclampsia (no further details provided)	17.5 *(57)*	12.3 *(57)*	1.52 (0.53-4.32)	-
Wimalasundera *et al.*, 2002(135)	Prospective Cohort	Two hospitals in London, UK (1990-2001)	214 HIV+ women and a single HIV- control for each HIV+ woman matched for age, parity and ethnic origin.	Only follows up women in ante-partum period	Yes	Pre-eclampsia defined according to Higgins and de Swiet(177)	4.2 *(214)*	5.6 *(214)*	0.74 (0.30-1.79)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Dystocia										
Chanrachakul *et al.*, 2001(157)	Retrospective Cohort	One tertiary hospital in Bangkok, Thailand (1991-1999)	All nulliparous HIV+ women delivering from 1991-1999 and all non-private, nulliparous HIV- women admitted in 1998. Excluded emergency c-section, deliveries before 37th week of gestation, multiple pregnancies or non cephalic presentation.	**HIV+**: 14.6% had a c-section **HIV-**: 15.0% had a c-section; analysis restricted to vaginal deliveries	No[1]	Prolonged labour defined as labour longer than 12 hours	29.2 *(82)*	5.0 *(1,540)*	7.86 (4.64-13.33)	-
Leroy *et al*., 1998(59)	Prospective Cohort	One tertiary hospital in Kigali, Rwanda (1992-1993)	All HIV+ women and one HIV- control for each HIV+ woman matched for age. Only included women resident in Kigali who attended antenatal clinic two days a week and wished to deliver in the hospital.	**HIV+**: 5.8% had a c-section **HIV-**: 6.0% had a c-section	No	Dystocia (no further details)	7.7 *(349)*	7.5 *(349)*	1.04 (0.59-1.82)	-
						Abnormal presentation (no further details)	7.0 *(356)*	5.6 *(360)*	1.28 (0.70-2.36)	-
Lionel *et al*., 2008(117)	Retrospective Cohort	One hospital in Vellore, India (2000-2002)	All HIV+ and HIV- women.	**HIV+**: 58.7% had a c-section **HIV-**: 21.5% had a c-section	Yes	Uterine Rupture (no further details)	0.9 *(109)*	0.3 *(23,277)*	2.75 (0.38-19.98)	-
Minkoff *et al.*, 1990(60)	Prospective Cohort	Four prenatal clinics in New York, USA (1985-1989)	All HIV+ women who had a live, singleton birth; in three of the prenatal clinics all HIV- women were also recruited, and in one of the clinics two HIV- controls were selected for each HIV+ woman.	**HIV+**: 12.0% had a c-section **HIV-**: 18.0% had a c-section	No	Abnormal presentation (no further details)	4.8 *(84)*	5.9 *(118)*	0.79 (0.22-2.80)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Wandabwa *et al.*, 2008(148)	Case-control	One hospital in Mulago, Uganada (2001-2002)	Case of ruptured uterus and controls were selected from women who had a gestation of 24 or more weeks, delivered a live, singleton baby by vaginal delivery, did not have episiotomy, tear of more than first degree or excessive blood loss.	All vaginal deliveries	No	Uterine rupture diagnosed both by clinical examination and at laparatomy	-	-	2.40 (1.10-4.20)	3.20 (1.50-7.20)[3]
Intrauterine infections										
Aboud *et al.* 2009(160)	Prospective Cohort (from an RCT)	Multiple hospitals and antenatal clinics in Malawi (Blantyre and Lilongwe) and Zambia (Lusaka) (2001-2003)	All HIV+ women enrolled and one HIV- woman enrolled for every five HIV+ women.	No information provided	No	Puerperal sepsis (no further details)	1.8 *(1,558)*	0 *(271)*	10.11 (0.62-166.11)	-
Chamiso, 1996(147)	Prospective Cohort	One maternity hospital in Addis Ababa, Ethiopia (1993-1995)	All HIV+ women and HIV- women matched to the HIV+ women for age and parity.	**HIV+**: 6.5% had a c-section **HIV-**: 9.2% had a c-section	No	Endometritis (no further details)	9.8 *(92)*	0 *(173)*	39.48 (2.27-686.46)	-
Chanrachakul *et al.*, 2001(157)	Retrospective Cohort	One tertiary hospital in Bangkok, Thailand (1991-1999)	All nulliparous HIV+ women delivering from 1991-1999 and all non-private, nulliparous HIV- women admitted in 1998. Excluded emergency c-section, deliveries before 37th week of gestation, multiple pregnancies or non cephalic presentation.	**HIV+**: 14.6% had a c-section **HIV-**: 15.0% had a c-section	No[1]	Puerperal infection (no further details)	1.0 *(96)*	1.0 *(1,856)*	1.02 (0.13-7.68)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Figueroa-Damian, 1999(120)	Prospective Cohort	Institute of Perinatology in Mexico City, Mexico (1989-1997)	44 HIV+ women and two HIV- controls for each HIV+ woman, matched on age and socioeconomic status.	**HIV+**: 29.9% had a c-section **HIV-**: 51.2% had a c-section	Yes	Endometritis (no further details)	0 *(44)*	4.6 *(88)*	0.21 (0.01-4.01)	-
Fiore *et al.*, 2004(159)	Prospective Cohort	14 references centres in Italy, Spain, Sweden, Poland and Ukraine (1992-2003)	HIV+ women were matched the first HIV- woman delivering after the infected index case on age ethnicity, parity and whether admitted to the delivery unit in active labour.	All vaginal deliveries	Yes	Endometritis (no further details)	4.4 *(250)*	2.0 *(250)*	2.26 (0.77-6.59)	-
Kourtis *et al.*, 2006(118)	Retrospective Cohort	20% of all community hospitals in the USA (1994 & 2003)	All HIV+ and HIV- pregnant women between 15-44 years of age who were hospitalised.	No information provided	Yes	Major puerperal sepsis identified using ICD-9 codes	2.9 *(12,378)*	0.9 *(8,784,767)*	3.37 (3.03-3.74)	-
Lepage *et al.* 1991(111)	Prospective Cohort	One hospital in Kigali, Rwanda (1988-1989)	All HIV+ women and an equal number of HIV- women matched for age and parity. Women had to have lived for at least six months in a district within a diameter of <10 Km from the hospital and delivered a live newborn.	No information provided	No	Endometritis (no further details)	0.9 *(215)*	0.9 *(216)*	1.00 (0.14-7.20)	-
Minkoff *et al.*, 1990(60)	Prospective Cohort	Four prenatal clinics in New York, USA (1985-1989)	All HIV+ women who had a live, singleton birth; in three of the prenatal clinics all HIV- women were also recruited, and in one of the clinics two HIV- controls were selected for each HIV+ woman.	**HIV+**: 12.0% had a c-section **HIV-**: 18.0% had a c-section	No	Endometritis (no further details)	4.4 *(91)*	2.4 *(126)*	1.89 (0.41-8.64)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Okong *et al.* 2004(149)	Case-control	One hospital in Kampala, Uganda (1996-1997)	For each case of postpartum endometritis and myometritis (PPEM), two controls without PPEM were randomly recruited, matched for mode of delivery.	Cases and controls were matched for mode of delivery	No	Endometritis defined as auxiliary temperature ≥38^{o}C on 2 different occasions 24 hours apart, with a tender uterus and foul-smelling or purulent vaginal discharge between delivery and 42 days postpartum	-	-	2.74 (1.34-5.65)	-
Onah *et al.*, 2007(151)	Retrospective Cohort	One university hospital in Enugu, Nigeria (2002-2004)	All HIV+ women and for every HIV+ woman the next two HIV- women who delivered were selected as controls.	**HIV+**: 8.1% had a c-section **HIV-**: 11.0% had a c-section	Yes	Puerperal sepsis (no further details)	8.1 *(62)*	0 *(100)*	19.23 (1.04-354.04)	-
Peret *et al*., 1993(143)	Prospective Cohort	One maternity hospital in Belo Horizonte, Brazil (2001-2003)	82 HIV+ women and 123 HIV- women matched for mode of delivery, gestational age at delivery and maternal age. Only included women if they did not have chronic diseases and/or complications of pregnancy.	**HIV+**: 72.0% had a c-section **HIV-**: 72.0% had a c-section	Yes	Endometritis defined as febrile morbidity with a tender uterus and/or foul-smelling vaginal discharge	4.9 *(82)*	0 *(123)*	14.16 (0.75-266.61)	-

Reference	Study design	Study Setting	Study Population	Mode of delivery in each study group	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Temmerman *et al.*, 1994(115)	Prospective Cohort	One health centre in Nairobi, Kenya (1989-1991)	All HIV+ women and a sample of HIV- women matched for age and parity to each HIV+ woman.	**HIV+**: 1.9% had a c-section **HIV-**: 3.8% had a c-section	No	Postpartum endometritis diagnosed if at ≥two of the following symptoms were present: fever of >38^{o}C, foul lochia and uterine tenderness	10.3 *(253)*	4.2 *(265)*	2.64 (1.28-5.47)	-

[1]Information was not supplied in the published paper so whether antiretroviral treatment should have been available was based on the study dates and study location; for two studies it was not clear from the study dates and location whether ART would be available so the information was inferred from the literature.

a) Bangkok, Thailand between 2001: No ART treatment based on the UNAIDS data accessed on 29th October 2012 at http://www.unaids.org/en/dataanalysis/datatools/aidsinfo/

b) Bloemfontein, South Africa in 2001: No ART treatment based on the UNAIDS data accessed on 29th October 2012 at http://www.unaids.org/en/regionscountries/countries/southafrica/

[2]Adjusted for smoking and cocaine use

[3]Adjusted for age, type of house, the distance from home to Mulago hospital, permission to attend health unit, person paying for hospital upkeep, previous length of labour and previous delivery by c-section

Table 4.2: Summary of studies of HIV and obstetric complications which only looked at births by caesarean section

Reference	Study design	Study Setting	Study Population	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Haemorrhage									
Chama and Morrupa, 2008(152)	Prospective Cohort	One university hospital in Maiduguri, Nigeria (2006)	All HIV+ women and an equivalent number of HIV- women who delivered by elective c-section.	Yes	Intra-operative haemorrhage defined as any bleeding during surgery requiring blood transfusion or a fall in packed cell volume ≥4%	23.1 *(52)*	40.4 *(52)*	0.44 (0.19-1.04)	-
Hypertensive diseases of pregnancy									
Chama and Morrupa, 2008(152)	Prospective Cohort	One university hospital in Maiduguri, Nigeria (2006)	All HIV+ women and an equivalent number of HIV- women who delivered by elective c-section.	Yes	Postpartum pregnancy-induced hypertension (no further details)	0 *(52)*	1.9 *(52)*	0.33 (0.01-8.21)	-
Sepsis									
Cavasin *et al.*, 2009(140)	Retrospective Cohort	Two health centres (one of which is part of a university hospital) in New Orleans in the USA (1998-2004)	All HIV+ women undergoing c-section; HIV- women were those who delivered by c-section during the same time period.	Yes	Post-operative endometritis defined as temperature elevation above 38^{o}C with uterine tenderness and requiring antibiotics treatment in the absence of other aetiology for fever	12.6 *(119)*	12.1 *(264)*	1.05 (0.54-2.01)	-
Chama and Morrupa, 2008(152)	Prospective Cohort	One university hospital in Maiduguri, Nigeria (2006)	All HIV+ women and an equivalent number of HIV- women who delivered by elective c-section.	Yes	Wound sepsis (not clearly defined)	3.8 *(52)*	5.8 *(52)*	0.65 (0.10-4.08)	-

Reference	Study design	Study Setting	Study Population	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Fiore *et al.*, 2004(159)	Prospective Cohort	14 references centres in Italy, Spain, Sweden, Poland and Ukraine (1992-2003)	All HIV+ women delivering by elective c-section were matched with the first HIV- woman delivering by elective c-section after the infected index case for age, ethnicity, parity, and whether admitted to the delivery unit in active labour.	Yes	Wound infection (no further details)	0.6 *(158)*	0 *(158)*	3.02 (0.12-74.67)	-
					Endometritis (no further details)	1.3 *(158)*	2.5 *(158)*	0.49 (0.09-2.73)	-
Grubert *et al*., 1999(136)	Retrospective Cohort	One medical facility in Germany (1987-1999)	All HIV+ women delivering by c-section were matched to an HIV- woman on age, duration of gestation and indication for caesarean.	Yes	Endometritis (no further details)	4.8 *(62)*	0 *(62)*	7.35 (0.37-145.40)	-
Louis *et al.*, 2007(119)	Prospective Cohort	19 different academic medical centres in the USA (1999-2002)	All women of known HIV status having a c-section at a gestational age of >20 weeks and who delivered a singleton infant of at least 500g birth weight.	Yes	Maternal sepsis defined as the presence of positive blood cultures and cardiovascular decompensation	1.1 *(378)*	0.2 *(54,281)*	6.98 (2.55-19.15)	6.2 (2.3-17.0)[2]
					Wound infection defined as erythema of the incision accompanied by purulent drainage requiring wound care	2.1 *(378)*	1.3 *(54,281)*	1.67 (0.83-3.39)	1.6 (0.8-3.3)[2]
					Endometritis defined as persistently elevated postpartum body temperature with uterine tenderness in the absence of a non-uterine source	11.6 *(378)*	5.8 *(54,281)*	2.14 (1.56-2.93)	1.9 (1.3-2.6)[2]

Reference	Study design	Study Setting	Study Population	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Maiques *et al.*, 2010(134)	Retrospective cohort	One referral hospital in Valencia, Spain (1997-2007)	All HIV+ women on ART and having a c-section; for every HIV+ woman the HIV- women who delivered by c-section before and after were selected as controls.	Yes	Wound infection or hematoma (no further details)	5.0 *(160)*	2.8 *(320)*	1.82 (0.69-4.81)	-
					Endometritis defined using clinical signs and a positive vaginal swab	0.6 *(160)*	0.6 *(320)*	1.00 (0.09-11.11)	-
Maiques-Montesinos *et al.*, 1999(65)	Retrospective Cohort	One maternity hospital in Valencia, Spain (1987-1996)	All HIV+ women delivering by c-section were matched to HIV- women for indication for c-section, stage of labour, number of foetuses and date of delivery.	No	Sepsis (no further details)	4.4 *(45)*	0 *(90)*	10.40 (0.49-221.37)	-
					Wound infection or hematoma (no further details)	26.7 *(45)*	6.7 *(90)*	5.09 (1.76-14.69)	-
					Endometritis (no further details)	2.2 *(45)*	4.4 *(90)*	0.49 (0.05-4.50)	-
Moodlier *et al.*, 2007(154)	Retrospective Cohort	One tertiary hospital in Durban, South Africa (2003-2004)	All women undergoing a c-section with known HIV status.	No[1]	Wound sepsis defined as the breakdown of the suture line as a result of a subcutaneous infectious process	5.4 *(186)*	8.0 *(175)*	0.65 (0.28-1.51)	-
					Endometritis defined as a sustained pyrexia (auxiliary temp greater than 38^{o}C) post-delivery (excluding the first 24 hours)	5.9 *(186)*	1.1 *(175)*	5.44 (1.19-24.89)	-

Reference	Study design	Study Setting	Study Population	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Panburana *et al.*, 2003(158)	Prospective Cohort	One tertiary hospital in Bangkok, Thailand (1999-2001)	Do not provide specific details on how HIV+ and HIV- women were selected but did exclude women who had a preterm delivery.	Yes	Endometritis (no further details)	2.7 *(74)*	1.7 *(360)*	1.64 (0.32-8.28)	-
Rodriguez *et al.*, 2001(141)	Prospective Cohort	One facility in the USA (no further details provided) (1992-2000)	All HIV+ women delivering by c-section were matched to an HIV- woman on age, race, year of delivery and indication for c-section.	Yes	Sepsis (no further details)	1.2 *(86)*	0 *(86)*	3.04 (0.12-75.55)	-
					Wound infection defined as purulent drainage, induration or tenderness	7.0 *(86)*	4.7 *(86)*	1.54 (0.42-5.65)	-
					Postpartum endometritis defined as a temperature >38^{o}C on two consecutive readings at an 8 hour interval, exclusive of the first 24 hours after delivery, with uterine tenderness, foul lochia, and no other apparent causes for fever	16.3 *(86)*	10.5 *(86)*	1.66 (0.68-4.08)	-
Semprini *et al.*, 1995(66)	Retrospective Cohort	Seven centres in Italy (1989-1993)	All HIV+ women delivering by c-section were matched to an HIV- woman on indication for c-section, active labour and whether they had ruptured membranes.	No	Sepsis (no further details)	0.6 *(156)*	0 *(156)*	3.02 (0.12-74.69)	-
					Wound infection (no further details)	8.3 *(156)*	1.9 *(156)*	4.64 (1.29-16.61)	-
					Febrile endometritis (no further details)	13.5 *(156)*	2.6 *(156)*	5.91 (1.98-17.65)	-

Reference	Study design	Study Setting	Study Population	ART Available	Definition of obstetric complication	% of HIV positive with obstetric complication *(total number of HIV+ women)*	% of HIV negative with obstetric complication *(total number of HIV+ women)*	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Urbani *et al.*, 2001(155)	Prospective Cohort	Two teaching hospitals in South Africa (1998)	307 women were enrolled irrespective of HIV status, and subsequently HIV status was ascertained. Women were excluded if they had diabetes mellitus.	No	Wound infection (no further details)	6.8 *(59)*	3.2 *(248)*	2.18 (0.63-7.51)	-
					Endometritis defined as fever of ≥38^{o}C on 2 occasions at least 4 hours apart and more than 24 hours post-operatively, tachycardia of >100 beats per minute on 2 occasions at least 4 hours apart and more than 24 hours post-operatively, and tenderness of the cervix on movement	23.7 *(59)*	6.9 *(248)*	4.23 (1.95-9.19)	-
Zvandasara *et al.*, 2007(153)	Prospective Cohort	One maternity hospital in Harare, Zimbabwe (2006)	All patients undergoing a c-section with known HIV status.	No	Wound infection was diagnosed in the presence of purulent discharge from the incision with induration and tenderness with or without fever	23.8 *(164)*	15.7 *(382)*	1.67 (1.06-2.63)	-
					Postpartum endometritis defined as temperature ≥38^{o}C on 2 successive readings at an 8 hour interval (excluding the 24 hours after delivery) and uterine tenderness, slight vaginal bleeding or foul smelling odour and no other apparent causes of fever	25.6 *(164)*	20.9 *(382)*	1.30 (0.85-1.99)	-

[1]Information was not supplied in the published paper so whether antiretroviral treatment should have been available was based on the study dates and study location; for one study it was not clear from the study dates and location whether ART would be available so the information was inferred from the literature.

a) Durban, South Africa in 2004: No ART treatment based on the UNAIDS data accessed on 20th December 2012 at http://www.unaids.org/en/regionscountries/countries/southafrica/

[2]Adjusted for number of previous caesarean section

Table 4.3: Risk of bias within studies which include vaginal deliveries

Reference	Definition of obstetric complication	Ascertainment of obstetric complication	Completeness of data	Adjustment for confounders	Selection of comparison group
HAEMORRHAGE					
Aboud *et al.* 2009(160) with supplementary information from (121)	No definitions provided for antepartum haemorrhage or postpartum haemorrhage	The pregnancy was followed prospectively, although it was not clear who collected the outcome data	6.9% of HIV+ women were lost to follow up compared with 7.6% of HIV- women	None	Unclear on exact selection methods; however no HIV- women were selected from one of the study sites
	High risk	**Unclear risk**	**Low risk**	**High risk**	**High risk**
Azria *et al.*, 2010(61)	Definition provided for postpartum haemorrhage	Hospital record review	Eight medical records of HIV+ women were missing data; no information for HIV- women	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	Low risk	**High risk**	**Unclear risk**	**Low risk**	**Low risk**
Braddick *et al.*, 1990(144)	Definition provided for antepartum haemorrhage	Hospital record review	0.6% of women refused to participate	None	HIV- Women were selected based on close proximity to the follow up clinic, but this selection criteria was not applied to HIV+ women
	Low risk	**High risk**	**Low risk**	**High risk**	**High risk**
Chamiso, 1996(147)	No definitions provided for placenta praevia, postpartum haemorrhage or retained placenta	Recorded by a general practitioner blinded to woman's HIV status	22% of HIV+ women were lost to follow up	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	High risk	**Low risk**	**High risk**	**Low risk**	**Low risk**

Reference	Definition of obstetric complication	Ascertainment of obstetric complication	Completeness of data	Adjustment for confounders	Selection of comparison group
Chanrachakul *et al.*, 2001(157)	No definitions provided for postpartum haemorrhage or retained placenta	Hospital record review	No information provided	None	HIV+ and HIV- women were enrolled from the same hospital; however HIV+ women were managed using traditional labour management and HIV- women were managed using active labour management
	High risk	**High risk**	**Unclear risk**	**High risk**	**High risk**
De Groot *et al.*, 2003(103)	Definitions provided for antepartum haemorrhage and postpartum haemorrhage	Hospital record review	2% of medical files selected into study were missing HIV status	None	HIV+ and HIV- women selected from the same hospital
	Low risk	**High risk**	**Low risk**	**High risk**	**Low risk**
Figueroa-Damian, 1999(120)	No definition provided for postpartum haemorrhage	The pregnancy was followed prospectively, although it was not clear who collected the outcome data	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	High risk	**Unclear risk**	**Unclear risk**	**Low risk**	**Low risk**
Haeri *et al.*, 2009(138)	No definition provided for placental abruption	Hospital record review	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same two tertiary care centres
	High risk	**High risk**	**Unclear risk**	**Low risk**	**Low risk**
Kourtis *et al.*, 2006(118)	ICD-9 codes were used to define antepartum haemorrhage	Hospital discharge data	No information provided	None[1]	HIV+ and HIV- women selected from the same hospitals
	Low risk	**High risk**	**Unclear risk**	**High risk**	**Low risk**
Leroy *et al*., 1998(59)	No definitions provided for postpartum haemorrhage or retained placenta	Recorded by a midwife blinded to woman's HIV status	5.2% refusal rate; 4.7% lost to follow up	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	High risk	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Lionel *et al*., 2008(117)	Placental abruption defined as grade III but no definitions for placenta praevia and PPH	Hospital record review	No information provided	None	HIV+ and HIV- women selected from the same hospital
	Unclear risk	**High risk**	**Unclear risk**	**High risk**	**Low risk**
Louis *et al.*, 2006(139)	No definition provided for postpartum haemorrhage	Hospital record review	No information provided	None	HIV+ and HIV- women selected from the same hospital
	High risk	**High risk**	**Unclear risk**	**High risk**	**Low risk**

Reference	Definition of obstetric complication	Ascertainment of obstetric complication	Completeness of data	Adjustment for confounders	Selection of comparison group
Minkoff *et al.*, 1990(60)	No definitions provided for placenta praevia, placental abruption, peripartum haemorrhage or retained placenta	Method of ascertaining outcome not clear	10% of HIV+ women refused to participate	None	HIV+ and HIV- women selected from the same clinics
	High risk	**Unclear risk**	**Low risk**	**High risk**	**Low risk**
Mmiro *et al*., 1993(112)	No definitions provided for antepartum haemorrhage or postpartum haemorrhage	Hospital record review	No information provided	None	HIV+ and HIV- women selected from the same hospital
	High risk	**High risk**	**Unclear risk**	**High risk**	**Low risk**
Peret *et al*., 1993(143)	Definition provided for postpartum haemorrhage	The pregnancy was followed prospectively, although it was not clear who collected the outcome data	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	Low risk	**Unclear risk**	**Unclear risk**	**Low risk**	**Low risk**
Van Eijk *et al*., 2007(145)	No definition provided for peripartum haemorrhage	Method of ascertaining outcome not clear	1.5% of women had missing data and were excluded	None	HIV+ and HIV- women selected from the same hospital
	High risk	**Unclear risk**	**Low risk**	**High risk**	**Low risk**
HYPERTENSIVE DISEASES OF PREGNANCY					
Aboud *et al.* 2009(160) with supplementary information from (121)	No definition provided for hypertension	The pregnancy was followed prospectively, although it was not clear who collected the outcome data	6.9% of HIV+ women were lost to follow up compared with 7.6% of HIV- women	None	Unclear on exact selection methods; however no HIV- women were selected from one of the study sites
	High risk	**Unclear risk**	**Low risk**	**High risk**	**High risk**
Bodkin *et al*., 2005(63)	No definitions provided for pregnancy-induced hypertension or eclampsia	Hospital record review	49.6% of women refused to be tested for HIV	HIV+ and HIV- women were only matched on whether their pregnancy was high-risk, medium-risk or low-risk	HIV+ and HIV- women selected from the same hospital
	High risk	**High risk**	**High risk**	**High risk**	**Low risk**
Boer *et al.*, 2006(137)	Definition provided for pre-eclampsia	Method of ascertaining outcome not clear	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same medical centres
	Low risk	**Unclear risk**	**Unclear risk**	**Low risk**	**Low risk**
Chamiso, 1996(147)	Definition provided from pregnancy-induced hypertension	Recorded by a general practitioner blinded to woman's HIV status	22% of HIV+ women were lost to follow up	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	Low risk	**Low risk**	**High risk**	**Low risk**	**Low risk**

Reference	Definition of obstetric complication	Ascertainment of obstetric complication	Completeness of data	Adjustment for confounders	Selection of comparison group
De Groot *et al*., 2003(103)	Definitions provided for pre-eclampsia and eclampsia	Hospital record review	2% of medical files selected into study were missing HIV status	None	HIV+ and HIV- women selected from the same hospital
	Low risk	**High risk**	**Low risk**	**High risk**	**Low risk**
Figueroa-Damian, 1999(120)	No definition provided for acute hypertensive disorder of pregnancy	The pregnancy was followed prospectively, although it was not clear who collected the outcome data	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	High risk	**Unclear risk**	**Unclear risk**	**Low risk**	**Low risk**
Frank *et al.*, 2004(64)	Definitions provided for pregnancy-induced hypertension and pre-eclampsia but not for eclampsia	Hospital record review	27% of files reviewed did not have known HIV status	None	HIV+ and HIV- women selected from the same hospital and clinics
	Unclear risk	**High risk**	**High risk**	**High risk**	**Low risk**
Haeri *et al.*, 2009(138)	Definition provided for pre-eclampsia but not for gestational hypertension	Hospital record review	No information provided	HIV+ and HIV- women were matched on key confounders and adjusted analysis conducted	HIV+ and HIV- women selected from the same two tertiary care centres
	Unclear risk	**High risk**	**Unclear risk**	**Low risk**	**Low risk**
Kourtis *et al.*, 2006(118)	ICD-9 codes were used to define pre-eclampsia/ hypertensive disorders of pregnancy	Hospital discharge data	No information provided	None[1]	HIV+ and HIV- women selected from the same hospitals
	Low risk	**High risk**	**Unclear risk**	**High risk**	**Low risk**
Lionel *et al.*, 2008(117)	No definitions provided for pre-eclampsia and eclampsia	Hospital record review	No information provided	None	HIV+ and HIV- women selected from the same hospital
	High risk	**High risk**	**Unclear risk**	**High risk**	**Low risk**
Mattar *et al*., 2004(100)	Definition provided for pre-eclampsia	Hospital record review	No information provided	None	HIV+ and HIV- women selected from the same clinic
	Low risk	**High risk**	**Unclear risk**	**High risk**	**Low risk**
Mmiro *et al*., 1993(112)	Definition provided for hypertension	Hospital record review	No information provided	None	HIV+ and HIV- women selected from the same hospital
	Low risk	**High risk**	**Unclear risk**	**High risk**	**Low risk**
Olagbuji *et al*., 2010(150)	No definition provided for pregnancy-induced hypertension	Method of ascertaining outcome not clear	No information provided	State that HIV- women were matched to HIV+ women but do not state what the matching characteristics were	HIV+ and HIV- women selected from the same hospital
	High risk	**Unclear risk**	**Unclear risk**	**Unclear risk**	**Low risk**

Reference	Definition of obstetric complication	Ascertainment of obstetric complication	Completeness of data	Adjustment for confounders	Selection of comparison group
Roman-Poueriet *et al*., 2009(142)	No definition provided for pregnancy-induced hypertension	Hospital record review	No information provided	None	Women were recruited from a range of public, private clinics and hospitals and a specialist HIV clinic
	High risk	**High risk**	**Unclear risk**	**High risk**	**Unclear risk**
Singh *et al.*, 2009(156)	No definition provided for pre-eclamptic toxaemia	States that the "antenatal complications in both study groups were observed"	No information provided	None	HIV+ and HIV- women selected from the same hospital
	High risk	**Unclear risk**	**Unclear risk**	**High risk**	**Low risk**
Suy *et al.*, 2006(133)	Definition provided for pre-eclampsia	Using a database	No information provided	Adjusted analysis was conducted but it is not clear what factors were adjusted for, therefore only the crude estimate was extracted	HIV+ and HIV- women selected from the same hospital
	Low risk	**High risk**	**Unclear risk**	**High risk**	**Low risk**
Waweru *et al*., 2009(146)	No definition provided for pre-eclampsia	Method of ascertaining outcome not clear	No information provided	None	HIV+ and HIV- women selected from the same hospital
	High risk	**Unclear risk**	**Unclear risk**	**High risk**	**Low risk**
Wimalasundera *et al*., 2002(135)	Definition provided for pre-eclampsia	Method of ascertaining outcome not clear	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospitals
	Low risk	**Unclear risk**	**Unclear risk**	**Low risk**	**Low risk**
DYSTOCIA					
Chanrachakul *et al.*, 2001(157)	Definition provided for prolonged labour	Hospital record review	No information provided	None	Although HIV+ and HIV- women were enrolled from the same hospital, HIV+ women were managed using traditional labour management and HIV- women were managed using active labour management
	Low risk	**High risk**	**Unclear risk**	**High risk**	**High risk**
Leroy *et al*., 1998(59)	No definitions provided for dystocia or abnormal presentation	Recorded by a midwife blinded to woman's HIV status	5.2% refusal rate; 4.7% lost to follow up	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	High risk	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Lionel *et al*., 2008(117)	No definition provided for uterine rupture	Hospital record review	No information provided	None	HIV+ and HIV- women selected from the same hospital
	High risk	**High risk**	**Unclear risk**	**High risk**	**Low risk**

Reference	Definition of obstetric complication	Ascertainment of obstetric complication	Completeness of data	Adjustment for confounders	Selection of comparison group
Minkoff *et al.*, 1990(60)	No definition provided for abnormal presentation	Method of ascertaining outcome not clear	10% of HIV+ women refused to participate	None	HIV+ and HIV- women selected from the same clinics
	High risk	**Unclear risk**	**Low risk**	**High risk**	**Low risk**
Wandabwa *et al.*, 2008(148)	Definition provided for uterine rupture	Cases of ruptured uterus were identified by clinical examination and at laparatomy	No information provided	Adjusted analysis conducted	HIV+ and HIV- women selected from the same hospital
	Low risk	**Low risk**	**Unclear risk**	**Low risk**	**Low risk**
INTRAUTERINE INFECTION					
Aboud *et al.* 2009(160) with supplementary information from (121)	No definition provided for puerperal sepsis	The pregnancy was followed prospectively, although it was not clear who collected the outcome data	6.9% of HIV+ women were lost to follow up compared with 7.6% of HIV- women	None	Unclear on exact selection methods; however no HIV- women were selected from one of the study sites
	High risk	**Unclear risk**	**Low risk**	**High risk**	**High risk**
Chamiso, 1996(147)	No definition provided for endometritis	Recorded by a general practitioner blinded to woman's HIV status	22% of HIV+ women were lost to follow up	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	High risk	**Low risk**	**High risk**	**Low risk**	**Low risk**
Chanrachakul *et al.*, 2001(157)	No definition provided for puerperal infection	Hospital record review	No information provided	None	Although HIV+ and HIV- women were enrolled from the same hospital, HIV+ women were managed using traditional labour management and HIV- women were managed using active labour management
	High risk	**High risk**	**Unclear risk**	**High risk**	**High risk**
Figueroa-Damian, 1999(120)	No definition provided for endometritis	The pregnancy was followed prospectively, although it was not clear how the outcome data was collected	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	High risk	**Unclear risk**	**Unclear risk**	**Low risk**	**Low risk**
Fiore *et al.*, 2004(159)	No definition provided for endometritis	Women were evaluated for the development of obstetric complications	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same delivering centres
	High risk	**Low risk**	**Unclear risk**	**Low risk**	**Low risk**
Kourtis *et al.*, 2006(118)	ICD-9 codes used to define major puerperal sepsis	Hospital discharge data	No information provided	None[1]	HIV+ and HIV- women selected from the same hospitals

Reference	Definition of obstetric complication	Ascertainment of obstetric complication	Completeness of data	Adjustment for confounders	Selection of comparison group
	Low risk	**High risk**	**Unclear risk**	**High risk**	**Low risk**
Lepage *et al.* 1991(111)	No definition provided for endometritis	Hospital record review	21% refusal rate; 16% of HIV- women and 21% of HIV+ women were lost to follow up	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	High risk	**High risk**	**High risk**	**Low risk**	**Low risk**
Minkoff *et al.*, 1990(60)	No definition provided for endometritis	Method of ascertaining outcome not clear	10% of HIV+ women refused to participate	None	HIV+ and HIV- women selected from the same clinics
	High risk	**Unclear risk**	**Low risk**	**High risk**	**Low risk**
Okong *et al.* 2004(149)	Definition provided for endometritis	Cases of endometritis were identified by midwives	8% of cases and controls refused to participate	None	HIV+ and HIV- women selected from the same hospital
	Low risk	**Low risk**	**Low risk**	**High risk**	**Low risk**
Onah *et al.*, 2007(151)	No definition provided for puerperal sepsis	Hospital record review	19% of HIV- women had to be excluded because their medical records could not be located	None	HIV+ and HIV- women selected from the same hospital
	High risk	**High risk**	**Low risk**	**High risk**	**Low risk**
Peret *et al.*, 1993(143)	Definition provided for endometritis	The pregnancy was followed prospectively, although it was not clear who collected the outcome data	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	Low risk	**Unclear risk**	**Unclear risk**	**Low risk**	**Low risk**
Temmerman *et al.*, 1994(115)	Definition provided for endometritis	Identified by a research nurse	2.3% women refused to participate; missing data for 38% of HIV+ and 35% of HIV- women on endometritis	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same health centre
	Low risk	**Low risk**	**High risk**	**Low risk**	**Low risk**

[1]**Adjusted odds ratios available for the data broken into two time periods; this data was not extracted**

Table 4.4: Risk of bias within caesarean section studies

Reference	Definition of obstetric complication	Ascertainment of obstetric complication	Completeness of data	Adjustment for confounders	Selection of comparison group
HAEMORRHAGE					
Chama and Morrupa, 2008(152)	Definition provided for intra-operative haemorrhage	No information provided	No information provided	None	HIV+ and HIV- women selected from the same hospital
	Low risk	**Unclear risk**	**Unclear risk**	**High risk**	**Low risk**
HYPERTENSIVE DISEASES OF PREGNANCY					
Chama and Morrupa, 2008(152)	No definition provided for pregnancy-induced hypertension	No information provided	No information provided	None	HIV+ and HIV- women selected from the same hospital
	High risk	**Unclear risk**	**Unclear risk**	**High risk**	**Low risk**
INTRAUTERINE INFECTION					
Cavasin *et al.*, 2009(140)	Definition provided for endometritis, but not for septic pelvic thrombosis	Hospital record review	No information provided	None	HIV+ and HIV- women selected from the same two health centres
	Unclear risk	**High risk**	**Unclear risk**	**High risk**	**Low risk**
Chama and Morrupa, 2008(152)	No definition provided for wound sepsis	No information provided	No information provided	None	HIV+ and HIV- women selected from the same hospital
	High risk	**Unclear risk**	**Unclear risk**	**High risk**	**Low risk**
Fiore *et al.*, 2004(159)	No definitions provided for wound infection or endometritis	Women were evaluated for the development of obstetric complications	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same delivering centres
	High risk	**Low risk**	**Unclear risk**	**Low risk**	**Low risk**
Grubert *et al*., 1999(136)	No definition provided for endometritis	Method of ascertaining outcome not clear	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same medical facility
	High risk	**Unclear risk**	**Unclear risk**	**Low risk**	**Low risk**
Louis *et al.*, 2007(119)	Definitions provided maternal sepsis, wound infection and endometritis	Method of ascertaining outcome not clear	No information provided	Adjusted analysis conducted	HIV+ and HIV- women selected from the same medical centres
	Low risk	**Unclear risk**	**Unclear risk**	**Low risk**	**Low risk**
Maiques *et al.*, 2010(134)	Definition provided for endometritis, but not for wound infection	Method of ascertaining outcome not clear	No information provided	None	HIV+ and HIV- women selected from the same hospital
	Unclear risk	**Unclear risk**	**Unclear risk**	**High risk**	**Low risk**

Reference	Definition of obstetric complication	Ascertainment of obstetric complication	Completeness of data	Adjustment for confounders	Selection of comparison group
Maiques-Montesinos *et al.*, 1999(65)	No definitions provided for sepsis, wound infection/haematoma or endometritis	Hospital record review	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	High risk	**High risk**	**Unclear risk**	**Low risk**	**Low risk**
Moodlier *et al.*, 2007(154)	Definitions provided wound sepsis and endometritis	Hospital record review	Only 1% of charts were missing, but state that about half of the women refused HIV testing	None	HIV+ and HIV- women selected from the same hospital
	Low risk	**High risk**	**High risk**	**High risk**	**Low risk**
Panburana *et al.*, 2003(158)	No definition provided for endometritis	Simply states that all complications were "recorded in both study and control groups"	No information provided	None	HIV+ and HIV- women selected from the same hospital
	High risk	**Unclear risk**	**Unclear risk**	**High risk**	**Low risk**
Rodriguez *et al.*, 2001(141)	Definition provided for endometritis and wound infection, but not for sepsis	Hospital record review	11% of HIV+ women did not have records available for review	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same hospital
	Unclear risk	**High risk**	**Low risk**	**Low risk**	**Low risk**
Semprini *et al.*, 1995(66)	No definitions provided for sepsis, wound infection or febrile endometritis	Method of ascertaining outcome not clear	No information provided	HIV+ and HIV- women were matched on key confounders	HIV+ and HIV- women selected from the same centres
	High risk	**Unclear risk**	**Unclear risk**	**Low risk**	**Low risk**
Urbani *et al.*, 2001(155)	Definition provided for endometritis but not for wound infection	Identified by a researcher	95% of women undergoing c-section were recruited	None	HIV+ and HIV- women selected from the same hospitals
	Unclear risk	**Low risk**	**Low risk**	**High risk**	**Low risk**
Zvandasara *et al.*, 2007 (153)	Definition provided for wound sepsis	Identified by a researcher	No patients were excluded	None	HIV+ and HIV- women selected from the same hospital
	Low risk	**Low risk**	**Low risk**	**High risk**	**Low risk**

4.3 CONCLUSION

We do not find evidence that the risk of obstetric complications is higher in HIV-infected women, with the exception of intrauterine infections. The increased risk of maternal sepsis and endometritis in HIV-infected women will contribute to the excess mortality attributable to HIV amongst pregnant and postpartum women, although this contribution in unlikely to be substantial as a relatively small percentage of pregnancy-related deaths are attributed to intrauterine infections.(178)

5 PREGNANCY AND HIV DISEASE PROGRESSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

5.1 INTRODUCTION

This chapter contains the results from the final systematic review, which aimed to address the third objective of this PhD by assessing whether pregnancy increases the risk of HIV disease progression. It updates a systematic review which was published in 1998.(51)

The draft paper presented here has been accepted by the journal Tropical Medicine and International Health, and is currently in press.

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NAME IN FULL (Block Capitals) CLARA CALVERT

STUDENT ID NO: 236162

CANDIDATE'S SIGNATURE ……..……. Date

SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above)

……..……

5.2 ARTICLE

5.2.1 Abstract

Background: Information on whether pregnancy is associated with HIV disease progression is needed to inform fertility choices in HIV-infected women. We conducted a systematic review to assess whether pregnancy accelerates HIV disease progression.

Methods: Studies comparing progression to HIV-related illness, low CD4 count, AIDS-defining illness, HIV-related death, or any death in HIV-infected pregnant and non-pregnant women were included. Relative risks (RR) for each outcome were combined using random-effects meta-analysis and were stratified by ART availability.

Results: Fifteen studies met the inclusion criteria. Pregnancy was not associated with progression to HIV-related illness [summary RR: 1.32, 95% confidence interval (CI): 0.66-2.61], AIDS-defining illness (summary RR: 0.97, 95%CI: 0.74-1.25) or mortality (summary RR: 0.97, 95%CI: 0.62-1.53) but there was an association with low CD4 counts (summary RR: 1.41, 95%CI: 0.99-2.02) and HIV-related death (summary RR: 1.65, 95%CI: 1.06-2.57). In settings where ART was available, there was no evidence that pregnancy accelerated progress to HIV/AIDS-defining illnesses, death, and drop in CD4 count. In settings without ART availability, effect estimates were consistent with pregnancy increasing the risk of progression to HIV/AIDS-defining illnesses and HIV-related or all-cause mortality, but there were too few studies to draw meaningful conclusions.

Conclusions: In the absence of ART, pregnancy is associated with small but appreciable increases in risk of several negative HIV outcomes, but the evidence is too weak to draw firm conclusions. When ART is available the effects of pregnancy on HIV disease progression are attenuated and there is little reason to discourage healthy HIV-infected women who desire to become pregnant from doing so.

5.2.2 Introduction

In 2000, the fifth Millennium Development Goal (MDG5) set a target of reducing maternal mortality by three-quarters between 1990 and 2015. As this deadline approaches there is evidence of worldwide progress, but countries in sub-Saharan Africa are lagging behind.(29, 32) The reasons for this are multiple, including high

fertility and health systems challenges, but the high burden of HIV is thought to be a key factor impairing progress.(10, 127) The contribution of HIV to maternal mortality is not well known, but around 25% of pregnancy-related deaths in sub-Saharan Africa may be attributable to HIV.(98, 171)

Quantifying the contribution of HIV to maternal mortality is challenging. Attributing a death in a pregnant or postpartum woman to HIV not only requires knowledge of the woman's HIV status, it also requires decisions about whether a death in an HIV-infected pregnant or postpartum woman is indirectly attributable or coincidental to the pregnancy (the latter are not classified as maternal deaths). Clinicians assigning causes of death classify most deaths in HIV-infected pregnant or postpartum women as indirectly attributable to the pregnancy, though justifications for this choice are rarely provided.(20, 179) In global-level mathematical models of maternal mortality varying assumptions are made about the proportion of deaths to HIV-infected pregnant and postpartum women which should be classified as maternal. The Institute of Health Metrics and Evaluation classifies all HIV/AIDS deaths in HIV-infected pregnant or postpartum women as attributable to pregnancy,(29) while the Maternal Mortality Estimation Interagency Group only considers 50% of such deaths as attributable to the pregnancy.(32) These assumptions are largely opinion based however, as there are few rigorous assessments of whether and to what extent HIV-related deaths during pregnancy are attributable rather than coincidental to the pregnancy.

Technically, the death of an HIV-infected pregnant or postpartum woman is attributable to the pregnancy if mortality in these women is in excess of what would be expected if the HIV-infected woman had not been pregnant. This can happen for two reasons, either because HIV increases the risk of direct obstetric complications, or because pregnancy accelerates the progression of HIV disease. A recent systematic review suggests that HIV does not increase the risk of direct obstetric complications, except for puerperal sepsis.(125) The empirical evidence in support of an acceleration of HIV disease progression during pregnancy is inconclusive. Some studies of HIV-infected women show that CD4 counts decrease faster during pregnancy;(47, 180) although one study found change in CD4 count rebounds in the postpartum period to match that of women who did not become pregnant.(180) A systematic review published in 1998 did not find evidence that pregnancy accelerates progression to an HIV-related illness or a low CD4 cell count, but did find weak evidence that the odds of acquiring an AIDS-defining illness or death were higher amongst HIV-infected pregnant than HIV-infected non-pregnant women.(51) An update of this review in 2009 suggested that there was

no effect of pregnancy on HIV disease progression, but only identified two additional studies and did not include a meta-analysis.(80)

Knowing whether pregnancy accelerates the progression of HIV also has relevance for the reproductive choices HIV-infected women make. Many HIV-infected women choose to become pregnant given the low risk of mother-to-child transmission and with the introduction of antiretroviral therapy (ART) which has enabled many HIV-infected women to lead long, healthy lives. However, this decision is made in the absence of conclusive data on whether pregnancy detrimentally affects their HIV disease progression, or whether ART modifies any association between pregnancy and HIV disease progression.

The aim of this paper is to systematically review the literature to examine whether pregnancy accelerates the progression of HIV. We compare HIV disease progression in pregnant and non-pregnant women of reproductive age and perform a meta-analysis of relative risks for low CD4 count, HIV-related illness, AIDS-defining illness, HIV-related death and any death. We also assess whether pooled relative risks vary by availability of ART, country income level and by whether studies used a risk or a hazard ratio.

5.2.3 Methods

Search Strategy and Inclusion Criteria

This systematic review adheres to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.(85) Searches of Pubmed, Embase, Popline and African Index Medicus were undertaken up to December 13, 2013 using MeSH and free-text terms for “pregnancy/ maternal”, “HIV/AIDS” and “progression” (full search strategy in Appendix A). There were no restrictions on language or year of publication. Reference lists of relevant articles were hand-searched to identify additional articles, including grey literature. Where necessary, authors of published studies were contacted to provide additional information.

Cohort and case-control studies, which allowed a comparison of the progression of HIV in pregnant and non-pregnant women, were eligible for inclusion. Studies were included regardless of the definition of the length of the pregnancy or postpartum period at risk. Progression of HIV was defined as: drop in CD4 count below a defined threshold, progression to an HIV-related illness (as defined by the authors),

progression to AIDS-defining illness (as defined by the authors), and progression to an HIV-related or any death. Conference abstracts were not eligible for inclusion.

Data Extraction and Quality Assessment

Data on study design, setting, year, sample size, study population, the definition and method of measuring HIV progression, the definition of pregnant and non-pregnant women, and the crude and adjusted effect estimates comparing HIV progression by pregnancy status were extracted from all eligible studies by C.C. using a standard protocol. For case-control studies the odds ratios (OR) were extracted. Where cohort studies used survival analyses to assess the association between pregnancy and HIV progression the hazard ratio (HR) or rate ratio (RaR) was extracted; otherwise the risk ratio (RiR) was taken. Information was also extracted on whether ART was widely available, partially available (i.e. available for only part of the study period), or not available. If data were duplicated across several publications we extracted data from the paper providing most information.

The risk of bias was determined using the component approach outlined by The Cochrane Collaboration(86) for a number of pre-defined quality criteria which were adapted from those used by French and Brocklehurst.(51) All studies were assessed on the following criteria:

1. Methods of ascertaining pregnancy status – high risk of bias if pregnant women were identified through self-report or clinical records rather than through a pregnancy test or through restriction to women who had given birth in hospital
2. Methods of defining non-pregnant group - high risk of bias if women who had been pregnant between HIV seroconversion and study entry could be classified as non-pregnant
3. Methods of ascertaining outcomes - high risk of bias if pregnant women were likely to be monitored more frequently than non-pregnant women
4. Length of follow-up - high risk of bias if pregnant and non-pregnant women were followed up for different lengths of time
5. Adjustment for differences in HIV stage or CD4 cell count in pregnant and non-pregnant women - high risk of bias if pregnant women were likely to be at a different stage of HIV infection during follow-up compared with non-pregnant women
6. Adjustment for key confounders - high risk of bias if no adjustments were made for confounders such as age and parity

If a study did not provide sufficient detail to be classified as high or low risk of bias for one of the quality criteria, then the risk of bias was deemed to be unclear.

Statistical Analyses

STATA version 13 was used to calculate pooled effect estimates comparing HIV disease progression in pregnant and non-pregnant women for each of the different measures of HIV disease progression. The DerSimonian and Laird random effects method was used to pool the effect estimates due to variation between study designs. Under the random effects model, summary effect estimates should be interpreted as an average of the study effect estimates which genuinely differ from one another. Where possible the adjusted HR was used as the effect estimate, and if that was not available the adjusted RiR or OR was used. Crude effect estimates were used if adjusted estimates were not presented. The I^2 value and p-value from the test of heterogeneity were calculated to assess whether there was evidence of between-study variation in the individual effect estimates which was not due to random variation.

Three sub-group analyses were planned *a priori* stratifying the pooled effect estimates by ART availability (partially/ widely available versus unavailable), by country income level(181) (high income versus not high income) and by the type of effect estimate (HR versus RiR). Meta-regression models were used to assess whether the sub-groups modified the pooled effect estimate.(86) Meta-analyses were conducted for each quality criterion, stratifying the pooled effect estimate by studies at high, low or unclear risk of bias.

Funnel plots were produced and the Egger funnel plot asymmetry test was conducted to assess whether there was publication bias for any of the outcomes.

5.2.4 Results

Study Selection and Characteristics

The search produced 21,744 citations and 20,237 of these were excluded through title and abstract screening (Figure 3.1). Of the 1,487 full-text papers which were reviewed, 15 contained relevant data. Three studies provided information on progression to an HIV-related illness,(182-184) four to an HIV-related death,(184-187) four to a CD4 count below a threshold level,(47, 182, 188, 189) nine to death,(47, 81, 180, 182, 183, 188-191) and ten to an AIDS-defining illness.(47, 81, 182-184, 187-189, 192, 193)

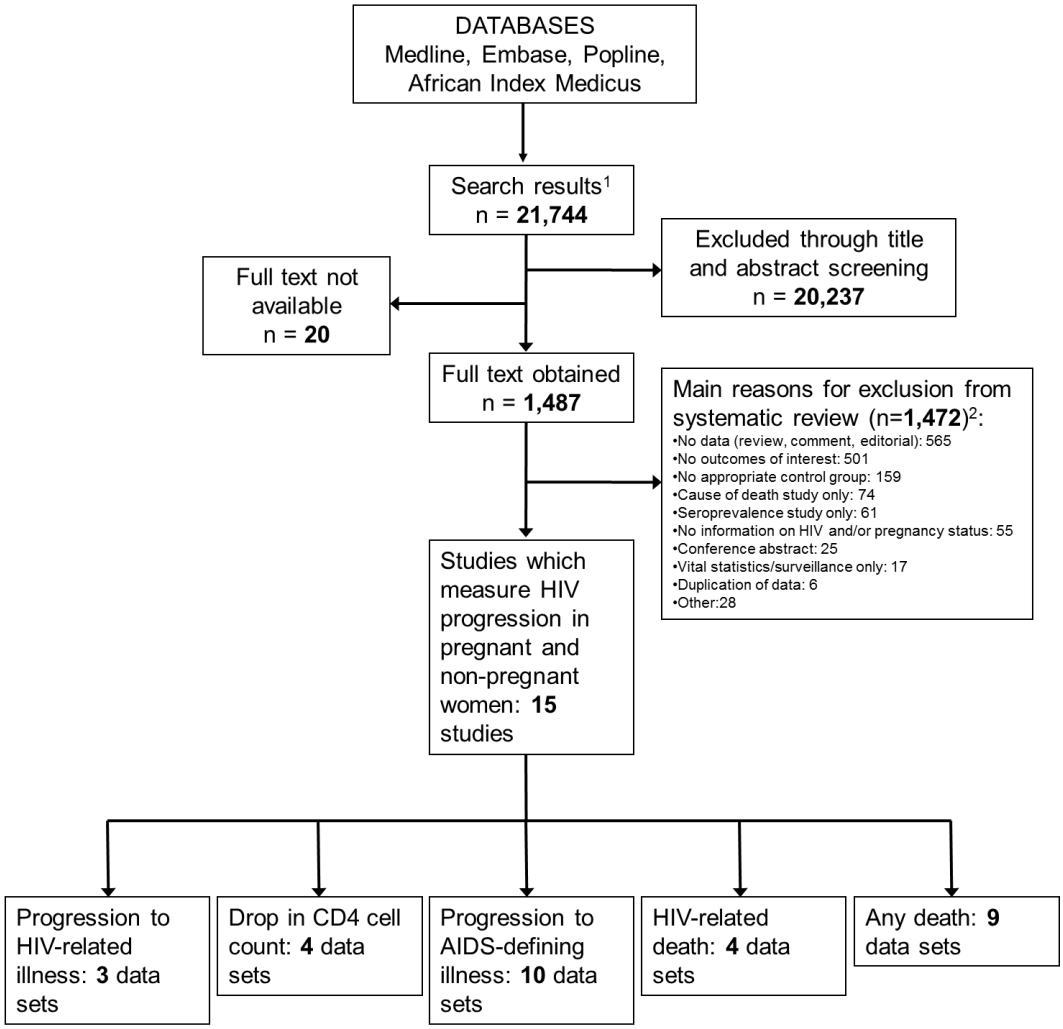

Figure 5.1: Flow chart of study selection for inclusion in the systematic review
[1]Total after removing duplicate references
[2]Articles may have been excluded for multiple reasons

AIDS-defining illnesses were defined according to CDC criteria in most studies (Table 5.1), but HIV-related illnesses included conditions as varied as weight loss, oral hairy leukoplakia and herpes zoster. HIV-related deaths were defined as deaths from AIDS(184, 186, 187) or HIV-related illnesses.(185) For progression to a CD4 count below a threshold level, two studies used a threshold of 200cells/µl(47, 188) and two used a threshold of 100cells/µl.(182, 189)

Table 5.1: Definitions for HIV progression

	Progression to an HIV-related illness	Drop in CD4 count	Progression to an AIDS-defining illness	Progression to an HIV-related deaths
Allen *et al.* 2007(185)	-	-	-	Women who were reported dead from HIV-related causes (no further details)
Alliegro *et al.* 1997(182)	Defined according to category B of the 1993 revised classification system for HIV infection[1]	Progression to a CD4 count of less than 100 cells/µl	Defined according to category C of the 1993 CDC classification system for HIV infection[1]	-
Berrebi *et al.* 1990(187)	-	-	Defined according to the 1987 CDC criteria[2]	Deaths were reported to be due to pneumocystosis and neurtoxoplasmosis
Bessinger *et al.* 1998(183)	Occurrence of oral thrush, herpes zoster or oral hairy leukoplakia	-	Defined according to the 1987 CDC criteria[2]	-
Buskin *et al.* 1998(192)	-	-	Defined according to category C of the 1993 CDC classification system for HIV infection[1]	-
Deschamps *et al.* 1993(184)	List the following HIV-related signs and symptoms in the results: Weight loss, fever>1 month, prurigo, generalised lymphadenopathy, herpes zoster, chronic cough, chronic diarrhoea and anogenital herpes	-	Defined according to the 1987 CDC criteria[2]	State that all the deaths in the study population stemmed from AIDS
Hocke *et al.* 1995(188)	-	Progression to a CD4 count of less than 200 cells/µl amongst women who had a CD4 count great than this at study entry	Defined according to both the 1987 and 1993 CDC criteria[1,2]	-
Kumar *et al.* 1997(186)	-	-	-	Women who died of AIDS-related illnesses
Matthews *et al.* 2013(190)	-	-	-	-
Mayanja *et al*.2012(180)	-	-	-	-
Saada *et al.* 2000(193)	-	-	Defined according to group C of the 1993 European classifiction[3]	-
Tai *et al.* 2007(81)	-	-	Defined according to category C of the 1993 CDC classification system for HIV infection[1]	-
Van der Paal *et al.* 2007(47)		Progression to a CD4 count of less than 200 cells/µl	Defined using the WHO staging system[4]	

Weisser *et al.* 1998(189)		Progression to a CD4 count of less than 100 cells/µl	Defined as occurrence of Pneumocystis carinii pneumonia, candida esophagitis, recurrent bacterial pneumonia, disseminated mycobacterium avium complex disease, cerebral toxoplasmosis, dementia, herpes simplex ulceration, wasting syndrome and other	
Westreich et al. 2013(191)	-	-	-	-

[1]1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recommendations and reports: Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control 1992; 41(RR-17): 1-19.

[2]Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. Council of State and Territorial Epidemiologists; AIDS Program, Center for Infectious Diseases. MMWR Morbidity and mortality weekly report 1987; 36 Suppl 1: 1S-15S.

[3]Revision de la definition du SIDA en France. Bull Epidemiol Hebd. 1993; 11: 47-48.

[4]Interim proposal for a WHO Staging System for HIV infection and Disease. Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations 1990; 65(29): 221-4.

The characteristics of each study are described in Table 5.6 (page 140). The studies were conducted in the USA,(81, 183, 192) France,(187, 188, 193) Italy,(182) Switzerland,(189) Haiti,(184) Rwanda,(185) Uganda,(47, 180, 190) South Africa(191) and India.(186) ART was not available in four studies,(47, 184, 185, 187) partially available in six studies,(182, 183, 188, 189, 192, 193) and widely available in five studies.(81, 180, 186, 190, 191)

All studies were cohorts, but there was extensive variation in how the “pregnant” and “non-pregnant” groups were defined. Of the 12 studies which allocated person-time pregnant, five considered pregnant and post-pregnancy time (regardless of length) as “pregnant”(182, 188, 189, 191, 193); two treated all person-time in women who became pregnant at any time during follow-up as “pregnant”(47, 81); one divided all person-time into three month intervals, and if a woman was pregnant at any time in the interval then that full period was classified as pregnant(185); one classified time spent pregnant and up to one year postpartum as “pregnant”(190); and one included all person-time of women who were pregnant during the baseline of the study as “pregnant”.(192) In the latter study, the “non-pregnant” person-time included both women who did not become pregnant and women who were not pregnant at baseline but became pregnant during follow-up. The remaining two studies did not provide

sufficient information to understand how the pregnant person-time was allocated.(183, 184)

Within the five studies not using person-time for at least one of the measures of HIV disease progression, the pregnant group was defined as women who were pregnant at baseline,(180, 186, 187) or at any time during follow-up.(182, 184) Only one of these studies had a fixed period of follow-up,(186) while another matched pregnant and non-pregnant woman on the length of follow-up.(187) Two studies had longer follow-up in pregnant than non-pregnant women, but did not present sufficient data for person-time to be calculated.(180, 184) One study did not provide information on the length of follow-up in pregnant and non-pregnant women, although did provide HRs for all outcomes except any death.(182)

Data Quality

None of the studies were judged to be at low risk of bias across all of the quality criteria (Table 5.7, page 145). Only three studies (20.0%) used robust methods to identify pregnancies,(47, 180, 188) while seven studies relied on either clinical records or self-report to identify pregnancies.(81, 182, 183, 185, 190-192) Five studies did not adequately describe the methods used to identify pregnancies.(184, 186, 187, 189, 193) Nine of the 11 studies enrolling HIV-infected women after seroconversion did not attempt to exclude HIV-infected women who had a pregnancy before study entry and women who had a pregnancy since HIV seroconversion could therefore be classified as non-pregnant.(81, 184-187, 190-193)

Eight studies had a longer length of follow-up in the pregnant than in the non-pregnant group.(81, 180, 183, 184, 188, 189, 191, 193) Nine studies were at high risk of following pregnant women more frequently compared with their non-pregnant counterparts.(81, 182, 183, 185, 188, 189, 191-193) Twelve studies adjusted for differences in HIV stage between pregnant and non-pregnant women. Six adjusted for HIV stage in the analysis: one used HIV clinical stage grouped into two categories(185); two studies used CD4 count as a continuous variable(190, 193); one grouped CD4 count into two categories(81) and two studies adjusted for CD4 count but did not provide more detail.(182, 192) One study used weighted models to adjust for HIV clinical stage and CD4 count (categories not specified).(191) Four studies matched pregnant and non-pregnant women on HIV stage: one study matched on HIV clinical stage but did not specify how this was categorised(187); one matched on CD4 count grouped into three categories(188) and two studies matched on CD4 count with no

further information on how this was grouped.(183, 186) The final study both matched on and adjusted for CD4 count grouped by 100cells/µl increments.(189) Only one study did not try to account for other key confounders such as age.(180) Two studies presented adjusted HRs for some outcomes while crude RiRs could only be extracted for other outcomes.(182, 184)

Pregnancy and HIV Progression

The strength of association between pregnancy and HIV progression is presented in Figure 5.2. Overall, pregnant women had 1.32 times the risk of developing an HIV-related illness compared with non-pregnant women; but the confidence interval (CI) was wide (95% CI: 0.66-2.61) and there was strong evidence for between-study heterogeneity (I^2: 77.1%, p=0.01). Pregnant women were at 1.41 times the risk of progressing to a low CD4 count compared with non-pregnant women (95% CI: 0.99-2.02, I^2=0%, p=0.83) but there was no evidence that pregnancy was associated with an increased risk of progression to an AIDS-defining illness (summary effect estimate: 0.97, 95% CI: 0.74-1.25, I^2=20.1%, p=0.26) or death (summary effect estimate: 0.97, 95% CI: 0.62-1·53, I^2=48.9%, p=0.05). There was, however, some evidence that pregnancy was associated with 1.65 times the risk of an HIV-related death (95% CI: 1.06-2.57) with low between-study heterogeneity (I^2=13.9%, p=0.32).

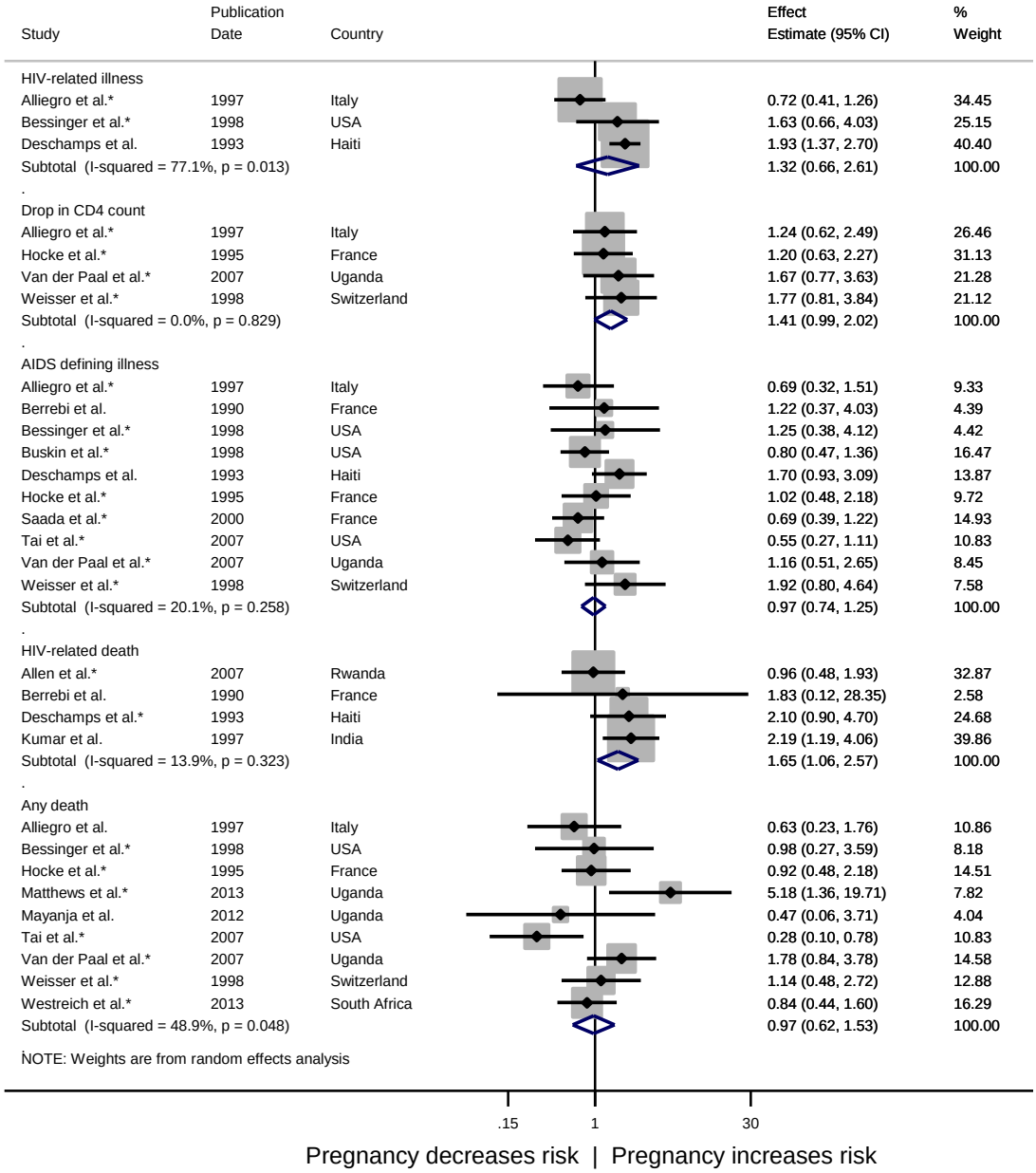

Figure 5.2: Forest plot showing the strength of association between pregnancy and HIV progression (includes all studies regardless of the effect estimate available)
***Adjusted estimates**

Effect of ART, Country Income, Type of Effect Estimate and Study Quality on the Strength of Association between Pregnancy and HIV Progression

Table 5.2 shows the pooled effect estimates for the different measures of HIV progression, stratified by whether ART was available or not. The pooled effect estimates were higher for progression to HIV-related illness, AIDS-defining illness, death, and drop in CD4 count before ART was available compared to settings where ART was available. Interactions by ART availability were only significant for progress to AIDS-defining illness (p=0.07) and death (p=0.05) where ten or nine studies were available for analysis. In these studies, there did not appear to be an association between pregnancy and death (summary effect estimate: 0.87, 95% CI: 0.54-1.41) or

AIDS-defining illness (summary effect estimate: 0.83, 95% CI: 0.63-1.08) once ART became available.

Table 5.2: Stratified analyses exploring the effect of antiretroviral therapy (ART) availability on the pooled effect estimate

	ART available	Number of studies	Pooled effect estimate (95% CI)	I^2	Coefficient[1] (95% CI)	P-value
Progression to an HIV-related illness	No	1	1.93 (1.37-2.70)	-	1	
	Yes	2	1.00 (0.46-2.19)	55.8	-0.83 (-9.80-8.15)	0.45
Drop in CD4 count	No	1	1.67 (0.77-3.63)	-	1	
	Yes	3	1.35 (0.90-2.02)	0	-0.30 (-2.22-1.61)	0.57
Progression to an AIDS-defining illness	No	3	1.45 (0.92-2.27)	0	1	
	Yes	7	0.83 (0.63-1.08)	2.8	-0.59 (-1.23-0.06)	0.07
Progression to an HIV-related death	No	3	1.35 (0.79-2.31)	3.2	1	
	Yes	1	2.19 (1.19-4.06)	-	0.67 (-2.88-4.21)	0.50
Progression to any death	No	1	1.78 (0.84-3.78)	-	1	
	Yes	8	0.87 (0.54-1.41)	44.8	-0.95 (-1.93-0.02)	0.05

Abbreviations: CI=confidence interval

[1]Change in pooled effect estimate between studies conducted when there was no ART (baseline) to those when there was ART available; note that the coefficient does not align exactly with the difference in the observed pooled effect estimate as in the meta-regression only one random effect is estimated, whereas in the subgroup analysis separate random-effects are calculated for each group

Stratifying by country income level did not reveal any distinct patterns beyond those observed for ART for progression to a low CD4 count, HIV-related illness or AIDS-defining illness (Table 5.3) as the study level measures of ART availability and country income level were closely correlated. There was no evidence that country income level modified the association between pregnancy and either progression to an HIV-related death (p=0.96) or progression to any death (p=0.41).

Table 5.3: Stratified analyses exploring the effect of country income level on the pooled effect estimate

		Number of studies	Pooled effect estimate (95% CI)	I^2	Coefficient[1] (95% CI)	P-value
Progression to an HIV-related illness	High Income	2	1.00 (0.46-2.19)	55.8	1	
	Not high income	1	1.93 (1.37-2.71)	-	0.83 (-8.15-9.80)	0.45
Drop in CD4 count	High Income	3	1.35 (0.90-2.02)	0	1	
	Not high income	1	1.67 (0.77-3.63)	-	0.30 (-1.61-2.22)	0.68
Progression to an AIDS-defining illness	High Income	8	0.84 (0.65-1.09)	0	1	
	Not high income	2	1.49 (0.92-2.42)	0	0.61 (-0.07-1.30)	0.07
Progression to an HIV-related death	High Income	1	1.83 (0.12-28.34)	-	1	
	Not high income	3	1.64 (0.96-2.80)	42.5	-0.08 (-6.85-6.69)	0.96
Progression to any death	High Income	5	0.74 (0.46-1.19)	19.7	1	
	Not high income	4	1.45 (0.65-3.27)	59.8	0.32 (-0.53-1.16)	0.41

Abbreviations: CI=confidence interval
[1]Change in pooled effect estimate between studies conducted in high income settings (baseline) compared to those conducted in non-high income settings; note that the coefficient does not align exactly with the difference in the observed pooled effect estimate as in the meta-regression only one random effect is estimated, whereas in the subgroup analysis separate random-effects are calculated for each group

Stratification by risk or a hazard ratio modified the relationship between pregnancy and progression to AIDS-defining illnesses (p=0.06), with studies using HRs showing lower effect estimates (Table 5.4).

Table 5.4: Stratified analyses exploring the effect of using risk ratio verses hazard ratios on the pooled effect estimate

	Study type	Number of studies	Pooled effect estimate (95% CI)	I^2	Coefficient[1] (95% CI)	P-value
Progression to an HIV-related illness	Risk ratio	1	1.93 (1.37-2.71)	-	1	
	Hazard ratio	2	1.00 (0.46-2.19)	55.8	-0.83 (-9.80-8.15)	0.45
Drop in CD4 count	Risk ratio	0	-	-		
	Hazard ratio	4	1.41 (0.99-2.02)	0	-	-
Progression to an AIDS-defining illness	Risk ratio	2	1.59 (0.93-2.72)	0	1	
	Hazard ratio	8	0.85 (0.66-1.10)	0	-0.69 (-1.41-0.02)	0.06
Progression to an HIV-related death	Risk ratio	2	2.17 (1.19-3.97)	0	1	
	Hazard ratio	2	1.37 (0.64-2.95)	50.4	-0.64 (-3.98-2.69)	0.50
Progression to any death	Risk ratio	2	0.60 (0.24-1.49)	0	1	
	Hazard ratio	7	1.06 (0.63-1.80)	58.2	0.41 (-0.83-1.65)	0.46

Abbreviations: CI=confidence interval
[1]Change in pooled effect estimate between studies reporting risk ratios (baseline) compared to those reporting hazard ratios; note that the coefficient does not align exactly with the difference in the observed pooled effect estimate as in the meta-regression only one random effect is estimated, whereas in the subgroup analysis separate random-effects are calculated for each group

Stratifying by study quality did not affect the findings (Table 5.5).

Table 5.5: Stratified analyses exploring the effect of study quality on the pooled effect estimate

	Low risk of bias		High risk of bias		Unclear risk of bias	
	N	Pooled estimate (95% CI)	N	Pooled estimate (95% CI)	N	Pooled estimate (95% CI)
Progression to HIV-related illness						
Ascertainment of pregnancy	0	-	2	1.00 (0.46-2.19)	1	1.93 (1.38-2.71)
Misclassifying a woman as not-pregnant	2	1.00 (0.46-2.19)	1	1.93 (1.38-2.71)	0	-
Ascertainment of outcome	1	1.93 (1.37-2.71)	2	1.00 (0.46-2.19)	0	-
Follow up	0	-	2	1.89 (1.38-2.60)	1	0.72 (0.41-1.26)
Adjustment for difference in HIV stage	2	1.00 (0.46-2.19)	0	-	1	1.93 (1.38-2.71)
Adjustment for other confounders	3	1.32 (0.66-2.61)	0	-	0	-
Drop in CD4 count						
Ascertainment of pregnancy	2	1.37 (0.84-2.25)	1	1.24 (0.62-2.48)	1	1.77 (0.81-3.85)
Misclassifying a woman as not-pregnant	4	1.41 (0.99-2.02)	0	-	0	-
Ascertainment of outcome	1	1.67 (0.77-3.63)	3	1.35 (0.90-2.02)	0	-
Follow up	0	-	2	1.40 (0.86-2.30)	2	1.42 (0.84-2.38)
Adjustment for difference in HIV stage	3	1.35 (0.90-2.02)	1	1.67 (0.77-3.63)	0	-
Adjustment for other confounders	4	1.41 (0.99-2.02)	0	-	0	-
Progression to AIDS-defining illness						
Ascertainment of pregnancy	2	1.08 (0.62-1.89)	4	0.73 (0.51-1.05)	4	1.24 (0.73-2.12)
Misclassifying a woman as not-pregnant	5	1.10 (0.75-1.61)	5	0.89 (0.59-1.33)	0	-
Ascertainment of outcome	3	1.45 (0.92-2.27)	7	0.83 (0.63-1.08)	0	-
Follow up	1	1.22 (0.37-4.03)	6	1.04 (0.68-1.58)	3	0.84 (0.57-1.23)
Adjustment for difference in HIV stage	8	0.84 (0.65-1.09)	1	1.16 (0.51-2.64)	1	1.70 (0.93-3.10)
Adjustment for other confounders	10	0.97 (0.74-1.25)	0	-	0	-
Progression to an HIV-related death						
Ascertainment of pregnancy	0	-	1	0.96 (0.48-1.93)	3	2.15 (1.32-3.49)
Misclassifying a woman as not-pregnant	0	-	4	1.65 (1.06-2.57)	0	-
Ascertainment of outcome	2	2.08 (0.94-4.58)	1	0.96 (0.48-1.93)	1	2.19 (1.19-4.06)
Follow up	3	1.50 (0.80-2.84)	1	2.10 (0.92-4.70)	0	-
Adjustment for difference in HIV stage	3	1.50 (0.80-2.84)	0	-	1	2.10 (0.92-4.70)
Adjustment for other confounders	4	1.65 (1.06-2.57)	0	-	0	-
Progression to any death						
Ascertainment of pregnancy	3	1.19 (0.67-2.12)	5	0.88 (0.40-1.93)	1	1.14 (0.48-2.71)
Misclassifying a woman as not-pregnant	5	1.10 (0.74-1.63)	3	0.99 (0.26-3.85)	1	0.47 (0.06-3.71)
Ascertainment of outcome	3	1.96 (0.69-5.54)	6	0.77 (0.54-1.11)	0	-
Follow up	1	5.18 (1.36-19.71)	6	0.78 (0.53-1.14)	2	1.13 (0.41-3.09)
Adjustment for difference in HIV stage	6	0.96 (0.53-1.73)	3	1.01 (0.44-2.34)	0	-
Adjustment for other confounders	7	1.06 (0.63-1.80)	2	0.60 (0.24-1.49)	0	-

Abbreviations: CI=confidence interval

Publication Bias

There was no evidence for publication bias for any outcomes except progression to a low CD4 count (p=0.03) (Figure 5.3) and any death (p=0.07) (Figure 5.4).

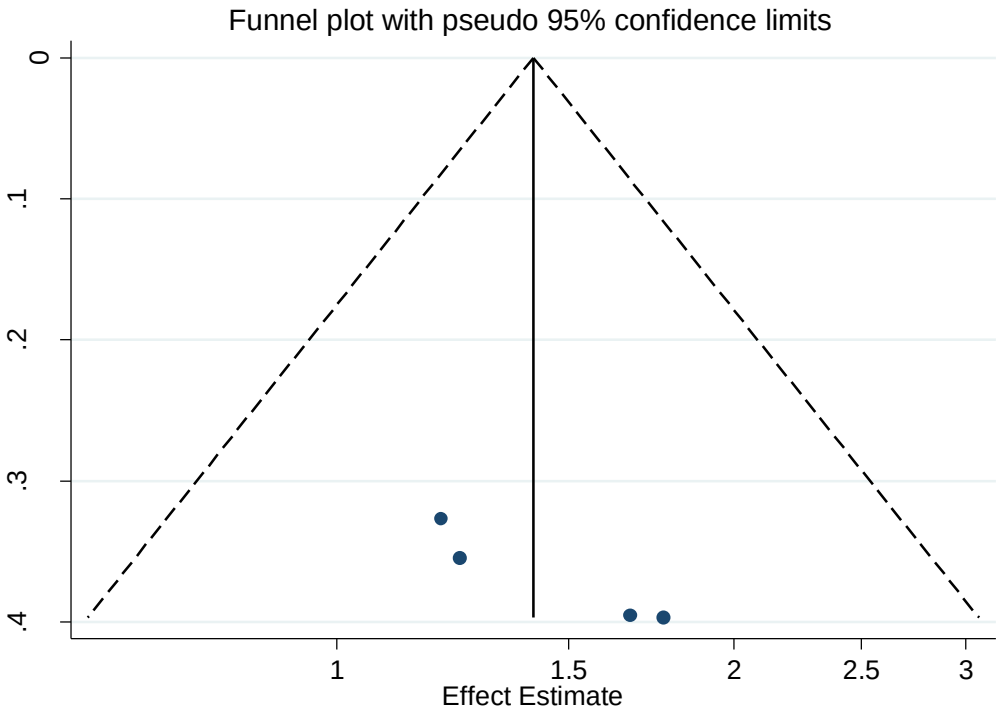

Figure 5.3: Funnel plot for studies measuring the effect of pregnancy on progression to a low CD4 count

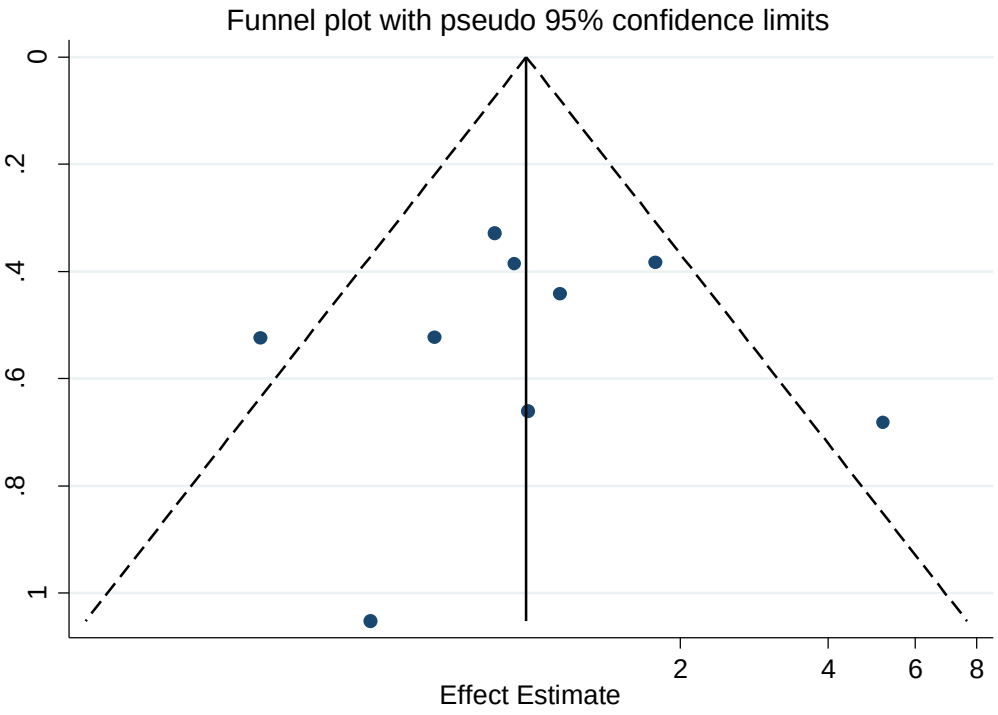

Figure 5.4: Funnel plot for studies measuring the effect of pregnancy on progression to any death

5.2.5 Discussion

In this systematic review we find no evidence that pregnancy is associated with accelerated progression to HIV-related illness, AIDS-defining illness, or all-cause mortality, though there is some evidence for acceleration to a drop in CD4 count and HIV-related death. In settings where ART was available, there was no evidence that pregnancy accelerated progress to HIV/AIDS-defining illnesses, death, and drop in CD4 count. In settings without ART availability, all the effect estimates were consistent with pregnancy increasing the risk of progression to HIV/AIDS-defining illnesses and HIV-related or all-cause mortality, but there were too few studies to draw meaningful conclusions.

One critical factor in interpreting disease or mortality rates comparing pregnant and non-pregnant women is the so-called “healthy pregnant woman effect” whereby healthier women are more likely to become pregnant.(194) Pregnant women may therefore appear healthier than non-pregnant women, even if pregnancy accelerates disease progression. This is particularly important for HIV, since women who are at a more advanced stage of HIV are less likely to become pregnant.(124) Most studies adjusted for or matched pregnant and non-pregnant women on HIV clinical stage or CD4 count; however some studies relied on very broad categorisations which may not fully account for the healthy pregnant woman effect. Furthermore, questions have been raised on the validity of using HIV clinical stage and CD4 cell count in pregnant and postpartum women, with studies showing that both these measures can be relatively insensitive to actual disease status.(195, 196) Therefore, pregnant women may still have been at an earlier stage of HIV progression compared with non-pregnant women.

Only three studies stratified their analyses by CD4 count: two found no association between pregnancy and HIV disease progression amongst women with either high or low CD4 count,(81, 188) while another study found much higher mortality in pregnant than in non-pregnant women with very low CD4 counts at time of ART initiation.(190) However, in the latter study, the five pregnant women who died were very ill at the time of recruitment, and it is uncertain whether these findings apply to the general population of pregnant HIV-infected women. Five studies excluded women who had a pregnancy not resulting in a live birth and/or going to term, which may also introduce a similar selection bias to the healthy pregnant woman effect if deteriorating health is associated with these adverse pregnancy outcomes.(183, 184, 187, 188, 193) Two of these found no difference in the level of immunosuppression comparing pregnancies which did or did not go to term,(183, 188) and one found no evidence for a difference in

the risk of HIV disease progression in women whose pregnancy terminated before 28 weeks, compared with women whose pregnancy continued.(187)

The main argument put forward in support of an adverse effect of pregnancy on HIV disease progression is that the systemic suppression of cell-mediated immunity during pregnancy may increase the susceptibility to or severity of infections.(38) Infectious diseases such as influenza, malaria, measles, and varicella are generally thought to be more severe during pregnancy.(37, 49, 197-202) However, these conclusions are largely based on clinical impressions, while the epidemiological evidence-base is scant. Very few studies, for example, assess how long the immuno-suppressive effects of pregnancy may persist into the postpartum period. In our review, only one study examined whether pregnancy itself increases the risk of HIV disease progression,(185) while most studies extended the exposure period to one year or more after birth, without separating the effects during pregnancy from those in the postpartum period or breaking down the postpartum period by time since pregnancy. Few studies clearly articulated how and for how long pregnancy may accelerate progression to HIV-related illness or death; and no study examined the effects of breastfeeding, which may increase the risk of mortality in HIV-infected women.(203) The lack of a clear conceptualisation of how pregnancy may affect HIV disease progression clearly impairs the interpretation of results.

When restricting the analysis to studies where ART was available, pregnant women appeared to have a slightly lower risk of death and progression to AIDS-related illnesses compared to non-pregnant women, although the confidence intervals were wide. Caution is required in interpreting such sub-group analyses, since we were not able to compare individual women with or without ART. Pregnant women tend to have greater contact with health services, may be more likely to be tested for HIV, and/or be eligible for ART at higher CD4 counts than non-pregnant women and may therefore have greater access to ART than the general population. This could partly explain the lack of effect of pregnancy on HIV disease progression with ART availability. Only four studies provided information on the proportion of pregnant and non-pregnant women receiving ART in their study population,(81, 189-191) however, and the effects were inconsistent.

The comprehensive search, with no restrictions by publication date, language or country, was a major strength of this systematic review. We identified an additional 12 studies compared to the previous systematic review of the effect of pregnancy on HIV disease progression.(51) There were, however, a number of limitations. There was

extensive between-study heterogeneity in studies looking at progression to HIV-related illnesses which was likely to be driven, in part, by the wide variation in the definitions of HIV-related diseases. However, in spite of the methodological differences between the studies, there was no evidence for extensive between-study heterogeneity for the other outcomes. We also combined risk ratios and hazard ratios in the meta-analysis, but stratification by risk or hazard ratios did not affect our summary effect estimates. Finally, as most of the included studies were not set up with the primary objective of evaluating the effect of pregnancy on HIV disease progression, the quality was generally poor, with no study judged to be at low risk of bias across all the quality criteria.

The methodological weaknesses of the studies highlight the need for high quality data examining whether pregnancy aggravates HIV progression. In particular, future studies need to ensure that the non-pregnant group excludes women who have been pregnant since HIV seroconversion, define the pregnancy period from the beginning of pregnancy onwards, and, where sample size permits, break down time post-pregnancy to establish how long any aggravating effects of pregnancy may persist. Because of concerns over the healthy pregnant woman effect, strict matching or adjustment for staging of the disease would be required. While it is unlikely that cohorts will be set up specifically for this purpose, ongoing HIV cohorts (for example (89) and (204)) should have this question in mind so that relevant data can be made available when necessary.

The findings of this review have implications for the definition and measurement of maternal mortality. If pregnancy does not aggravate HIV disease, most of the excess mortality in HIV-infected pregnant women (98, 171) is probably coincidental to pregnancy and HIV/AIDS-related deaths should not be counted as maternal deaths. If pregnancy does aggravate HIV disease then some of the excess mortality in HIV-infected pregnant women is attributable to HIV/AIDS and some (though not all) HIV/AIDS-related deaths should be counted as maternal. However, since the effect of pregnancy on HIV disease progression may vary by ART availability, interpretation of whether or not an HIV/AIDS-related death should be counted as maternal will now depend on context, and each death will have to be assessed individually. To avoid this complexity, some authors have suggested that restricting the definition of maternal mortality to direct obstetric causes may provide a clearer focus for assessing the impact of Safe Motherhood programmes.(205) However, measuring the contribution of HIV to mortality in pregnancy or postpartum is important, not in the least because some HIV-associated deaths during pregnancy or postpartum may be preventable with timely

access to ART antenatally. As such, pregnancy-related mortality, which counts all deaths in HIV-infected pregnant and postpartum women regardless of attribution, may be the preferred indicator for monitoring progress towards reducing mortality in pregnancy and the postpartum.

Our findings have some implications for the reproductive choices of HIV-infected women. In the absence of ART, pregnancy is associated with small but appreciable increases in risk of several negative HIV outcomes, but the evidence is too weak to draw firm conclusions. When ART is available the effects of pregnancy on HIV progression are attenuated, and there is little reason to discourage a healthy, HIV-infected woman who desires to become pregnant from doing so provided adequate counselling is available on how to prevent HIV transmission to her partner and baby, and there is ready access to ART from the period of conception until the end of breastfeeding.

Table 5.6: Description of studies which compare HIV progression in pregnant and non-pregnant women

	Study setting	Study population: Inclusion criteria	Study population: Pregnant	Study population: Non-pregnant	ART available	Median length of follow up	Definition of HIV progression	Median time to event	Crude effect estimate (95% CI)	Adjusted effect estimate (95% CI)
Allen *et al.* 2007(185) with further details provided by the author	Tertiary hospital in Kigali, Rwanda (1988-1994)	Women aged 18 to 35.	Person-time was split into 3-month intervals and if the woman was pregnant at any point in the 3-month interval then that period of time was classified as pregnant.	Person-time was split into 3-month intervals and if the woman was not pregnant throughout the whole interval then the interval was classified as non-pregnant.	No	All participants followed-up for six years, with an overall loss to follow-up of 10%	Progression to an HIV-related death	Not stated	HR: 0.87 (0.44-1.72)	HR: 0.96 (0.48-1.93)[1]
Alliegro *et al.* 1997(182)	14 clinical centres in Italy (1981-1994)	Women with a known date of seroconversion.	Person-time after conception in 69 women who had a least one pregnancy.	Person-time between HIV seroconversion and conception for 69 women; for the 262 women who did not conceive all time was classified as non-pregnant.	Partially	Not stated	Progression to HIV-related illness	Not stated	HR: 0.82 (0.48-1.42)	HR: 0.72 (0.41-1.26)[2]
							Progression to AIDS-defining illness	Not stated	HR: 0.74 (0.34-1.58)	HR: 0.69 (0.32-1.51)[2]
							Progression to a CD4 count of less than 100 cells/µl	Not stated	HR: 1.08 (0.57-2.08)	HR: 1.24 (0.62-2.49)[2]
							Progression to any death	Not stated	RR: 0.63 (0.23-1.76)[3]	-
Berrebi *et al.* 1990(187)	One university hospital in Toulouse, France (1985-1989)	Women in clinical stage II or III (Centre for Disease Control AIDS classification), excluding those with a pregnancy ending before 28 weeks gestation.	35 women who had a pregnancy. These women were followed-up from the termination of their pregnancy.	64 women who had never been pregnant or had terminated their last pregnancy at least two years before entry to the study.	No	Pregnant: 17 months Non-pregnant: 16 months	Progression to AIDS-defining illness	Not stated	RR: 1.22 (0.37-4.03)	-
							Progression to HIV-related death	Not stated	RR: 1.83 (0.12-28.35)	-

	Study setting	Study population: Inclusion criteria	Study population: Pregnant	Study population: Non-pregnant	ART available	Median length of follow up	Definition of HIV progression	Median time to event	Crude effect estimate (95% CI)	Adjusted effect estimate (95% CI)
Bessinger *et al.* 1998(183)	Medical clinic in New Orleans, USA (1988-1996)	Women aged 15- 35 years with at least 12 months follow-up, excluding women who had a pregnancy not ending in a live birth.	45 women who had a pregnancy after testing positive for HIV and after clinic entry, although unclear whether pre-pregnancy person-time was excluded from the "pregnant" group,	45 women who did not have a pregnancy after testing positive for HIV, although unclear whether pre-pregnancy person-time was included in the "non-pregnant" group.	Partially	Pregnant: 32 months Non-pregnant: 20 months	Progression to HIV-related illness	Not stated	HR: 1.27 (0.60-2.71)	HR: 1.63 (0.66-4.03)[4]
							Progression to AIDS-defining illness	Not stated	HR: 1.56 (0.58-4.16)	HR: 1.25 (0.38-4.12)[4]
							Progression to any death	Not stated	HR: 0.86 (0.33-2.24)	HR: 0.98 (0.27-3.59)[4]
Buskin *et al.* 1998(192)	Nine outpatient clinics in Seattle, USA (?-1997)	Women who did not have AIDS at the start of the study, were less than 49 years old and had more than one month follow-up.	Person-time of 83 women who were pregnant at baseline.	Person-time of 289 women who were not pregnant at baseline (including 26 women who became pregnant during the follow-up period).	Partially (study finished in 1997 but start date not provided)	35 months	Progression to AIDS-defining illness	Not stated	-	HR: 0.80 (0.47-1.36)[5]
Deschamps *et al.* 1993 (184)	Haiti (1984-1988)	Women aged 15 to 45, who were asymptomatic for HIV at entry to study, excluding three women who had a pregnancy which was not viable.	44 women who had a least one pregnancy during the study period; all post pregnancy time included in the pregnant group but unclear whether pre-pregnancy person-time was included in the "pregnant" group for the hazard ratio.	96 women who were not pregnant during the study period and either had never been pregnant or had their last delivery ≥12 months before study entry; unclear whether pre-pregnancy was included in the "non-pregnant" group for the hazard ratio.	No	Pregnant: 51 months Non-pregnant: 41 months	Progression to HIV-related illness	Pregnant: 20 months Non-pregnant: 19 months	RR: 1.93 (1.37-2.70)	-
							Progression to AIDS-defining illness	Pregnant: 35 months Non-pregnant: 33 months	RR: 1.70 (0.93-3.09)	-
							Progression to HIV-related death	Pregnant: 49 months Non-pregnant: 45 months		HR: 2.1 (0.9-4.7)[6]
Hocke *et al.* 1995 (188)	One university hospital in Bordeaux, France	Women aged 15 to 45 years, excluding women who had	Person-time from beginning of pregnancy in 57 women who had	114 women who had not conceived since being diagnosed with HIV	Partially (ART available from	Pregnant: 61 months Non-pregnant: 50 months	Progression to AIDS-defining illness	Not stated		HR: 1.02 (0.48-2.18)[7]

	Study setting	Study population: Inclusion criteria	Study population: Pregnant	Study population: Non-pregnant	ART available	Median length of follow up	Definition of HIV progression	Median time to event	Crude effect estimate (95% CI)	Adjusted effect estimate (95% CI)
	(1985-1994)	a pregnancy not ending in a live birth.	at least one pregnancy since HIV diagnosis; authors state that pregnancy was treated as a time dependant variable so assume pre-pregnancy time was excluded.	matched to pregnant women on age, CD4 count and diagnosis period; for hazard ratio assume person-time preceding first conception classified as "non-pregnant".	1989)		Progression to a CD4 count of less than 200 cells/µl	Not stated		HR: 1.20 (0.63-2.27)[7]
							Progression to any death	Not stated		HR: 0.92 (0.48-2.18)[7]
Kumar *et al.* 1997(186)	A tertiary hospital in Manipur, India (1992-1996)	Women with AIDS.	32 women who were pregnant at entry into the study.	39 women who were not pregnant at entry into the study.	Widely	Four years	Progression to HIV-related death	Pregnant: 9.7 months Non-pregnant: 22.6 months	-	RR: 2.19 (1.19-4.06)
Matthews *et al.* 2013(190)	Mbara University HIV clinic, Uganda (2005-2011)	Women aged 18-49.	Person-time after pregnancy was first reported up to one year postpartum in 109 women who became pregnant.	Person-time spent not pregnant or up to one year postpartum in 109 women who became pregnant; for the 245 women who did not conceive all time was classified as non-pregnant.	Widely (all women had been on ART for one year)	Four years	Progression to any death	State that median time from ART initiation to death in non-pregnant woman was 8.5 months. No information for pregnant women.	Rate Ratio: 3.56 (0.97-11.07)	HR: 5.18 (1.36-19.71)[8]
Mayanja *et al.*2012(180)	South-west Uganda (2004-2009)	Women aged 20 to 40.	23 women who became pregnant during follow-up.	65 women who did not become pregnant during the study.	Widely	Pregnant: 3·1 years Non-pregnant: 2·1 years	Progression to any death	Time to death was 0.5 years for the one pregnant woman who died. Time to death ranged from between 0.1 and 2.2 years for the non-pregnant women.	RR: 0.47 (0.06-3.71)	-

	Study setting	Study population: Inclusion criteria	Study population: Pregnant	Study population: Non-pregnant	ART available	Median length of follow up	Definition of HIV progression	Median time to event	Crude effect estimate (95% CI)	Adjusted effect estimate (95% CI)
Saada *et al.* 2000(193)	Numerous hospitals and obstetric departments throughout France (1988-1997)	Women aged 45 years or less who had a documented date of seroconversion, excluding women who had a pregnancy which did not go to term.	Person-time after conception in 241 women.	Person-time between HIV-seroconversion and first conception for 241 women; for the 124 women who did not conceive while HIV-infected all time was classified as non-pregnant.	Partially	Pregnant: 39 months Non-pregnant: 65 months	Progression to AIDS-defining illness	Not stated	HR: 0.69 (0.41-1.18)	HR: 0.69 (0.39-1.22)[9]
Tai *et al.* 2007(81) with further clarification from [(206)]	A comprehensive care centre in Tennessee, USA (1997-2004)	Women who had either a CD4 count and/or HIV RNA level available from a test obtained up to 120 days before, but no later than 365 days after the initial clinic visit during the study period.	All person time of 139 women who had a pregnancy at any time during follow-up	All person time of 620 women who did not have a pregnancy during follow-up	Widely (100% of pregnant and 77% of non-pregnant women on ART)	Pregnant: 58 months Non-pregnant: 33 months	Progression to AIDS-defining illness	Not stated		HR: 0.55 (0.27-1.11)[10]
							Progression to any death	Not stated		HR: 0.28 (0.10-0.78)[10]
Van der Paal *et al.* 2007(47) with further details provided by the author	South-West Uganda (1990-2003)	Women aged 15 to 49.	All person-time of 22 women who had only one pregnancy since HIV seroconversion.	All person-time of 58 women who did not have a pregnancy after HIV seroconversion.	No	Not stated	Progression to AIDS-defining illness	Pregnant: 10.4 years Non-pregnant: 8.2 years	-	HR: 1.16 (0.51-2.65)[11]
							Progression to a CD4 count of less than 200 cells/µl	Pregnant: 4.9 years Non-pregnant: 6.0 years	-	HR: 1.67 (0.77-3.63)[11]
							Progression to any death	Pregnant: 7.8 years Non-pregnant: 6.8 years	-	HR: 1.78 (0.84-3.78)[11]
Weisser *et al.* 1998(189)	Various university centres and hospitals in	Women aged 19 to 35 years at registration who had a CD4 count	Person time from conception in 32 women who had a pregnancy during	Person-time from enrolment of 416 women who did not conceive during the	Partially (1% of pregnant and 3% of	Pregnant: 60 months Non-pregnant: 55 months	Progression to AIDS-defining illness	Not stated	-	HR: 1.92 (0.80-4.64)[12]

	Study setting	Study population: Inclusion criteria	Study population: Pregnant	Study population: Non-pregnant	ART available	Median length of follow up	Definition of HIV progression	Median time to event	Crude effect estimate (95% CI)	Adjusted effect estimate (95% CI)
	Switzerland (1985-1995)	available before pregnancy, excluding women who terminated their pregnancy by induced abortion and women pregnant before study entry.	the study period.	study matched to the pregnant women on age, year of enrolment to study and CD4 count at entry to study.	non-pregnant women on ART)		Progression to a CD4 count of less than 100 cells/µl	Not stated	-	HR: 1.77 (0.81-3.84)[12]
							Progression to any death	Not stated	-	HR: 1.14 (0.48-2.72)[12]
Westreich et al, 2013(191)	A single hospital in Johannesburg, South Africa (2004-2011)	Previously HAART naive women aged 18-45 who were starting HAART treatment and were not pregnant at the baseline of the study.	All person-time following the start of the first pregnancy which occurred during follow up in 918 women.	Person-time between study entry and first pregnancy during follow-up in 918 women; for the 6616 women who did not have a pregnancy reported during follow-up all time was classified as non-pregnant.	Widely	2.1 years	Progression to any death	Time to death in pregnant group: 15 months; no information provided for non-pregnant group.	HR: 0.67 (0.43-1.05)	HR: 0.84 (0.44-1.60)[13]

Abbreviations: ART=antiretroviral therapy, HAART= highly active ART, RR=risk ratio, HR=hazard ratio, CI=confidence interval

[1]Adjusted for lifetime number of pregnancies, breastfeeding, oral contraceptive use, injectable contraceptive use, HIV disease stage, age and knowledge of French

[2]Adjusted for age at seroconversion, exposure group (heterosexual vs. Injecting drug user), most recent CD4 count, ART and *Pneumocystis carinii* pneumonia prophylaxis

[3]Demonator number of women rather than person-years

[4]Adjusted for age and ethnicity

[5]Adjusted for baseline CD4 count, clinical category (symptomatic or asymptomatic non-AIDS), age, HIV risk category (injecting drug user, no identified risk and other), year of enrolment*, Pneumocystis carinii* pneumonia prophylaxis, *Mycobacterium avium-intracellulare complex* prophylaxis and ART

[6]Adjusted for age and parity

[7]Adjusted for Centers for Disease Control and Prevention group of human immunodeficiency virus infection, CD4 count, age and calendar year at the time of HIV diagnosis

[8]Adjusted for time-updated age, CD4 count and plasma HIV-1 RNA level

[9]Adjusted for age at seroconversion, the baseline CD4 cell percentage, and the way in which seroconversion was dated

[10]Adjusted for CD4 count, HIV-1 RNA level, age and durable virologic suppression

[11]Adjusted for age at seroconversion

[12]Adjusted for CD4 count at entry
[13]Weighted models which account for age, employment status, active tuberculosis at study entry, calendar date at entry, WHO stage, and baseline and time-updated measures of weight, body mass index, haemoglobin, CD4 count and percent, adherence, and current drug regimen

Table 5.7: Assessment of the quality of the studies

	EXPOSURE		OUTCOME	FOLLOW-UP	CONFOUNDING	
	Ascertainment of pregnancy	**Risk of incorrectly classifying a woman as not pregnant when she had been pregnant since HIV seroconversion**	**Ascertainment of outcome(s)**	**The extent of follow up by pregnancy group (person time)**	**Adjustment for differences in HIV stage in pregnant and non-pregnant group[1]**	**Adjustment for other key confounders**
Allen *et al.* 2007(185) with further details provided by the author	Self-reported by woman at interviews six months apart	No information on HIV seroconversion and no attempt to exclude women who were pregnant before the study began from the non-pregnant group	Deaths reported by family members; symptoms around death taken from hospital/outpatient records or from family report at 6-monthly interviews	90% follow-up rate after six years	Adjust for HIV disease stage at study entry (two categories: Stage I/II and Stage III/IV)	Also adjust for lifetime number of pregnancies, breastfeeding, oral contraceptive use, injectable contraceptive use, age, and knowledge of French
	High risk	**High risk**	**High risk (clinical data)**	**Low risk**	**Low risk**	**Low risk**
Alliegro *et al.* 1997(182)	Clinical record	Known dates of seroconversion so should correctly classify all pregnancies since HIV-infection in pregnant group	Not clear; state that data came from clinical centres	No information	Adjust for most recent CD4 count (except when looking at the outcome: progression to any death) (categories not specified)	Also adjust for age at seroconversion, exposure group (heterosexual vs. injecting drug user), ART, and *Pneumocystis carinii* pneumonia prophylaxis (except when looking at the outcome: progression to any death)
	High risk	**Low risk**	**High risk**	**Unclear risk**	**Low risk**	**Low risk**
Berrebi *et al.* 1990(187)	Not clear	No information on HIV seroconversion; the non-pregnant group included women who terminated their last pregnancy at least 2 years prior to entering the study	Follow-up by one of the study authors; data collected at pre-defined follow-up points	Non-pregnant women were matched to pregnant women on length of follow-up	Non-pregnant women were matched to pregnant women on stage of HIV disease (categories not specified)	Pregnant and non-pregnant group were matched on age
	Unclear risk	**High risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**

	EXPOSURE		OUTCOME	FOLLOW-UP	CONFOUNDING	
	Ascertainment of pregnancy	**Risk of incorrectly classifying a woman as not pregnant when she had been pregnant since HIV seroconversion**	**Ascertainment of outcome(s)**	**The extent of follow up by pregnancy group (person time)**	**Adjustment for differences in HIV stage in pregnant and non-pregnant group[1]**	**Adjustment for other key confounders**
Bessinger *et al.* 1998(183)	Clinical records	Known dates of seroconversion so should correctly classify all pregnancies since HIV-infection in pregnant group	From clinic database and through the AIDS surveillance program at the Louisiana State office of Public Health	Follow up was longer in pregnant than in non-pregnant women (32 vs. 20 months)	Pregnant and non-pregnant group were matched on closest CD4 count at entry to clinic (categories not specified)	Adjust for ethnicity and age
	High Risk	**Low risk**	**High risk**	**High risk**	**Low risk**	**Low risk**
Buskin *et al.* 1998(192)	Medical record review	No information on HIV seroconversion. Only classify women as pregnant if they were pregnant at baseline of study; women who were pregnant before the start of study or became pregnant after the start of the study would be classified as non-pregnant	Medical record review	No information on whether follow-up varied by pregnancy group	Adjust for CD4 count at the start of follow-up (categories not specified)	Also adjust for clinical category (symptomatic or asymptomatic non-AIDS), age, HIV risk category (injecting drug user, no identified risk and other), year of enrolment, *Pneumocystis carinii* pneumonia prophylaxis, *Mycobacterium avium-intracellulare complex* prophylaxis, and ART
	High risk	**High risk**	**High risk**	**Unclear risk**	**Low risk**	**Low risk**
Deschamps *et al.* 1993(184)	Unclear how pregnancy status was ascertained	No information on HIV seroconversion; the non-pregnant group include women who had their last delivery at least 12 months before study entry	Follow-up visits same in the pregnant and non-pregnant group	Six patients lost to follow-up; longer follow up in the pregnant than in the non-pregnant group (51 vs. 41 months)	No attempt to take into account differences in HIV stage but do state that a sample of pregnant and non-pregnant women had similar β_2-microglobulin serum levels at study entry	Adjust for age and parity
	Unclear risk	**High risk**	**Low risk**	**High risk**	**Unclear risk**	**Low risk**
Hocke *et al.* 1995 (188)	Women who gave birth in Bordeaux University Hospital in pregnant group	Known dates of seroconversion so should correctly classify all pregnancies since HIV-infection in pregnant group	Questionnaires administered at every consultation or hospitalisation	26 patients lost to follow up; Longer follow-up in pregnant than in the non-pregnant group (61 vs. 50 months)	Pregnant women were matched to non-pregnant women on CD4 count (three categories: >500, 200-500 and <200 cells/µl)	Pregnant and non-pregnant group were matched on age and year of HIV diagnosis

	EXPOSURE		OUTCOME	FOLLOW-UP	CONFOUNDING	
	Ascertainment of pregnancy	**Risk of incorrectly classifying a woman as not pregnant when she had been pregnant since HIV seroconversion**	**Ascertainment of outcome(s)**	**The extent of follow up by pregnancy group (person time)**	**Adjustment for differences in HIV stage in pregnant and non-pregnant group[1]**	**Adjustment for other key confounders**
	Low risk	**Low risk**	**High risk**	**High risk**	**Low risk**	**Low risk**
Kumar *et al.* 1997(186)	No information	Do not have HIV seroconversion dates and do not state that they excluded women who had previously been pregnant from the non-pregnant group	Do not provide information on the frequency of follow-up visits or the methods used to collect the outcome data	Follow-up should have been four years in both groups; state that they achieved follow up in all patients	Restricted to women who had AIDS and matched pregnant and non-pregnant women on CD4 count (categories not specified)	Pregnant and non-pregnant group were also matched on age, parity and "demographic characteristics"
	Unclear risk	**High risk**	**Unclear risk**	**Low risk**	**Low risk**	**Low risk**
Matthews *et al.* 2013(190)	Self-reported by woman at quarterly interviews	Women entering the study reported whether they were currently pregnant but did not report on dates of pre-enrolment pregnancy or postpartum status	Follow-up visits scheduled every 6 months. If contact was not made with a participant within 6 months of a scheduled visit then HIV clinic records were reviewed and family members were contacted to identify deaths.	State that loss to follow up did not differ between women who were pregnant and those who did not have a pregnancy	Adjust for CD4 count (continuous) and viral load suppression (< vs. ≥400 copies/ml) both treated as time dependant covariates	Also adjust for age
	High risk	**High risk**	**Low risk**	**Low risk**	**Low risk**	**Low risk**
Mayanja *et al.*2012(180)	At all follow up visits urine pregnancy testing was performed	It is not clear if they exclude women who may have been pregnant and HIV-infected before enrolment into the cohort	Participants attended the clinic for three monthly routine visits, where a clinician administered a medical and sexual history questionnaire and undertook a full physical examination	Longer follow-up in pregnant than in the non-pregnant group (3·1 vs. 2·1 years)	None	None
	Low risk	**Unclear risk**	**Low risk**	**High risk**	**High risk**	**High risk**

	EXPOSURE		OUTCOME	FOLLOW-UP	CONFOUNDING	
	Ascertainment of pregnancy	**Risk of incorrectly classifying a woman as not pregnant when she had been pregnant since HIV seroconversion**	**Ascertainment of outcome(s)**	**The extent of follow up by pregnancy group (person time)**	**Adjustment for differences in HIV stage in pregnant and non-pregnant group[1]**	**Adjustment for other key confounders**
Saada *et al.* 2000(193)	No information	Estimate dates of seroconversion but do not exclude women who might have been pregnant between seroconversion and study enrolment from the non-pregnant group[2]	Women are examined every 3/6 months depending on clinical status and whether pregnant or not	Longer follow-up in the non-pregnant than in the pregnant group (65 vs. 39 months)	Adjust for CD4 count at study entry (CD4 percentage was treated as continuous)	Also adjust for age at infection and the seroconversion dating method
	Unclear risk	**High risk**	**High risk**	**High risk**	**Low risk**	**Low risk**
Tai *et al.* 2007(81)	Clinical data were entered into an electronic medical record by medical providers at the time of patient encounter	No information on HIV seroconversion and no attempt to exclude women who were pregnant before the study began from the non-pregnant group	Clinical data were entered into an electronic medical record by medical providers at the time of patient encounter	Longer follow-up in the pregnant than in the non-pregnant group (58 vs. 33 months)	Adjusted for CD4 count at study entry (two categories: >200 and ≤200 cells/μl)	Also adjust for HIV-1 RNA level, age, and durable virologic suppression
	High risk	**High risk**	**High risk**	**High risk**	**Low risk**	**Low risk**
Van der Paal *et al.* 2007(47) with further details provided by the author	Study participants are seen routinely every three months by one of two study physicians who ask about date of last mensus and reasons for any amenorrhoea	Only include women who seroconverted during the study period so should correctly classify all pregnancies since HIV-infection in pregnant group	Study participants are seen routinely every three months by one of two study physicians who perform clinical examinations	No information	None	Adjust for age at seroconversion
	Low risk	**Low risk**	**Low risk**	**Unclear risk**	**High risk**	**Low risk**

	EXPOSURE		OUTCOME	FOLLOW-UP	CONFOUNDING	
	Ascertainment of pregnancy	**Risk of incorrectly classifying a woman as not pregnant when she had been pregnant since HIV seroconversion**	**Ascertainment of outcome(s)**	**The extent of follow up by pregnancy group (person time)**	**Adjustment for differences in HIV stage in pregnant and non-pregnant group[1]**	**Adjustment for other key confounders**
Weisser *et al.* 1998(189)	State that pregnancies, abortions and deliveries are recorded prospectively, but no information on how this data is collected	Excluded women who were pregnant before study entry	Follow up visits scheduled every 6 months and questionnaire is used to identify new and recurring HIV-associated diseases; additional data from a second study where pregnant HIV-infected women have 3-monthly visits	Longer follow-up in the pregnant than in the non-pregnant group (60 vs. 55 months)	Tried to match pregnant and non-pregnant women on CD4 count at study entry (categorised by increments of 100 cells/µl) but pregnant women did have a higher mean CD4 count than controls so also adjusted for CD4 count at entry (categorised by increments of 100 cells/µl)	Pregnant and non-pregnant group were matched on age
	Unclear risk	**Low risk**	**High risk**	**High risk**	**Low risk**	**Low risk**
Westreich et al, 2013(191)	Identified from clinical records and records of antiretroviral drug regimens	Do not exclude women who may have been pregnant and HIV-infected before enrolment into the cohort	Deaths were obtained from the clinic database and from the national death registry	Pregnant woman were less likely to be loss to follow-up compared with non-pregnant women	Weighted models accounted for WHO stage (categories not specified), and baseline and time-updated measures of CD4 count and percent (categories not specified)	Weighted models accounted for age, employment status, active tuberculosis at study entry, calendar date at entry, and baseline and time-updated measures of weight, body mass index, haemoglobin, adherence, and current drug regimen
	High risk	**High risk**	**High risk**	**High risk**	**Low risk**	**Low risk**

Abbreviations: ART=antiretroviral therapy, WHO= World Health Organization
[1]In particular whether matching for time since HIV diagnosis or a measure of immune function occurred
[2]A second estimate is available from the paper which includes women with unknown dates of seroconversion date but excludes women who had been pregnant before enrolment to the study

5.3 CONCLUSION

This review suggests that, where ART is available, almost all deaths attributable to HIV in pregnant and postpartum women are likely to be coincidental to the pregnancy. In settings where ART is not available, we do see small increases in the risk of HIV disease progression with pregnancy. The interpretation of these results are tricky as, on the one hand, the confidence intervals are wide but, on the other hand, all but one study report relative risks consistent with an excess risk with pregnancy. If we assume that this increased risk is real then we can extrapolate to calculate the percentage of HIV/AIDS-related deaths which should be classified as indirect maternal deaths. We find, for example, that the risk of an HIV-related death is 1.35 times higher in pregnant compared to non-pregnant women; we can therefore predict that approximately 25% of HIV/AIDS-related deaths should be classified as indirect causes of maternal death (i.e. out of 135 deaths to pregnant and postpartum women, 35 will have been aggravated by pregnancy).

So far the results presented in this thesis have relied on published data which has been largely facility-based, and concerns have been raised about study quality across all the reviews. In the next two chapters population-based data from sub-Saharan Africa will be used to further explore the effect of HIV on pregnancy-related mortality.

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6 EFFECT OF HIV INFECTION ON PREGNANCY-RELATED MORTALITY IN SUB-SAHARAN AFRICA: SECONDARY ANALYSES OF POOLED COMMUNITY BASED DATA FROM THE NETWORK FOR ANALYSING LONGITUDINAL POPULATION-BASED HIV/AIDS DATA ON AFRICA (ALPHA)

6.1 INTRODUCTION

This chapter presents the results of analyses estimating the effect of HIV on pregnancy-related mortality using community-based data from six of the member sites of the ALPHA network. The key findings from this work were written up as an article and published in the Lancet Women Deliver series.(171) This article is presented in Section 6.2; however, some of the results which were originally included in the appendix of the paper have been integrated into the body of the text.

Following on from the article are the results from a number of additional analyses which were undertaken to test the sensitivity of the results which were published. In the final section of this chapter the implications of these results are discussed.

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   I am the second author on this paper. I was responsible for preparing the data for analyses alongside Milly Marston, conducting the statistical analyses (with the exception of calculating the HIV prevalence and general fertility rates which were done with help from Milly Marston), and writing the first draft of the introduction, methods and results sections of the paper.

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6.2 ARTICLE

6.2.1 Abstract

Background: Model-based estimates of the global proportions of maternal deaths that are in HIV-infected women range from 7% to 21%, and the effects of HIV on the risk of maternal death is highly uncertain. We used longitudinal data from the Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA) network to estimate the excess mortality associated with HIV during pregnancy and the postpartum period in sub-Saharan Africa.

Methods: The ALPHA network pooled data gathered between June, 1989 and April, 2012 in six community-based studies in eastern and southern Africa with HIV serological surveillance and verbal autopsy reporting. Deaths occurring during pregnancy and up to 42 days postpartum were defined as pregnancy-related. Pregnant or postpartum person-years were calculated for HIV-infected and HIV-uninfected women, and HIV-infected to HIV-uninfected mortality rate ratios and HIV-attributable rates were compared between pregnant or postpartum women and women who were not pregnant or postpartum.

Findings: 138,074 women aged 15-49 years contributed 636,213 person-years of observation. 49,568 women had 86,963 pregnancies. 6,760 of these women died, 235 of them during pregnancy or the postpartum period. Mean prevalence of HIV infection across all person-years in the pooled data was 17.2% [95% confidence interval (CI) 17.0-17.3], but 60 of 118 (50.8%) of the women of known HIV status who died during pregnancy or postpartum were HIV-infected. The mortality rate ratio of HIV-infected to HIV-uninfected women was 20.5 (95% CI: 18.9-22.4) in women who were not pregnant or postpartum and 8.2 (95% CI: 5.7-11.8) in pregnant or postpartum women. Excess mortality attributable to HIV was 51.8 (95% CI: 47.8-53.8) per 1,000 person-years in women who were not pregnant or postpartum and 11.8 (95% CI: 8.4-15.3) per 1,000 person-years in pregnant or postpartum women.

Interpretation: HIV-infected pregnant or postpartum women had around eight times higher mortality than did their HIV-uninfected counterparts. On the basis of this estimate, we predict that roughly 24% of deaths in pregnant or postpartum women are attributable to HIV in sub-Saharan Africa, suggesting that safe motherhood

programmes should pay special attention to the needs of HIV-infected pregnant or postpartum women.

6.2.2 Introduction

Indicators for measuring progress towards the Millennium Development Goals include maternal mortality (the fifth Millennium Development Goal) and HIV/AIDS-associated mortality (the sixth Millennium Development Goal). In sub-Saharan Africa, the high prevalence of HIV infection in pregnant women makes the interaction between HIV and maternal mortality an important public health issue. In the 2011 follow-up of the UN General Assembly, a specific goal on HIV and maternal mortality was set i.e., to halve HIV mortality in pregnant or postpartum women by 2015.(175) The substantial increase in adult mortality because of HIV, which has been noted in many studies in sub-Saharan Africa,(207, 208) might have an adverse effect on pregnancy-related mortality even if the link between HIV and maternal death is not causal, and affects the reliability of assessments of progress towards the fifth Millennium Development Goal.

Although recent estimates have suggested that maternal mortality is decreasing worldwide, worrying increases have been noted in some countries in sub-Saharan Africa. WHO estimates that the maternal mortality ratio increased by more than 40% in all countries in southern Africa between 1990 and 2005.(29, 32) In Zimbabwe and Malawi the MMR increased by a factor of 2.5 and 1.8 respectively between 1985-94 and 1995-99.(10) Reasons for these increases are poorly understood. The increasing prevalence of HIV infection is thought to be the main driver, (29, 32) but empirical evidence supporting this assertion is weak.

The contribution of HIV to maternal mortality can be measured by calculating the proportion of maternal deaths attributed to HIV. A systematic review of population-based studies published between 1997 and 2002 examining the cause distribution of maternal deaths showed that 6.2% of maternal deaths in Africa can be attributed to HIV/AIDS (based on eight Africa-based studies).(101) Most studies that have been published so far are facility-based. Some hospital-based studies(18-20, 209) in areas where the prevalence of HIV infection is high have shown that HIV/AIDS is one of the leading causes of pregnancy-related deaths. In a tertiary hospital in South Africa, more than 40% of maternal deaths were loosely attributed to HIV/AIDS,(20) and, in a 2012 analysis(210) of all institutional maternal deaths in South Africa in 2008–10, 70% were in HIV-infected women. Because of the scarcity of empirical data for the interaction

between HIV and maternal mortality, most estimates of the contribution of HIV to maternal mortality rely on mathematical models with inbuilt assumptions about how HIV interacts with pregnancy. A model developed by the Institute of Health Metrics and Evaluation assumed that all deaths in HIV-infected pregnant or postpartum women should be classified as maternal; as a result, roughly 20.5% of maternal deaths in 2011 were attributed to HIV globally.(29) Another model, which was produced by the UN Maternal Mortality Estimation Inter-agency Group, assumed that only 50% of deaths in HIV-infected pregnant or postpartum women were maternal; 6.5% of the global maternal deaths in 2010 were estimated to be attributable to HIV/AIDS on the basis of this model.(32)

An alternative measure of the contribution of HIV to mortality during pregnancy is the excess mortality associated with HIV in pregnant or postpartum women. On the basis of a systematic review of 23 studies, 17 of which were done in sub-Saharan Africa, HIV-infected pregnant or postpartum women were estimated to have nearly eight times the risk of death that non-HIV-infected women had.(98) The authors of the review, which was focused on pregnancy-related mortality rather than maternal mortality, used this risk ratio to predict that roughly 25% of pregnancy-related deaths in sub-Saharan Africa were attributable to HIV.

The paucity of empirical data for the effect of HIV on mortality during pregnancy is largely the result of difficulties with methods. In most community-based studies, the HIV status of women and girls who die is unknown, and very few maternal deaths are encountered. We use longitudinal data from the network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA), which links ten HIV community-based cohort studies(211) from eastern and southern Africa (six of which have the necessary data), to calculate the excess mortality associated with HIV during pregnancy and the postpartum period.

6.2.3 Methods

Study design

We used data from six independently established studies in Karonga, Kisesa, Manicaland, Masaka, Rakai, and uMkhanyakude in our analysis. Fieldwork methods for each study have been described in detail elsewhere.(97, 212-216) Briefly, the studies recorded demographic data—ie, dates of births (of both mothers and infants), deaths, and, except for Karonga and Rakai, dates of pregnancy reports. Each study also

provided dates and results of HIV tests for their surveillance populations. In Karonga, Kisesa, Rakai, and uMkhanyakude, the demographic and HIV surveys were done separately, and data were linked via unique personal identifiers. In Manicaland and Masaka, household censuses were administered to record demographic events and list eligible participants for HIV testing immediately before serological surveillance.

HIV test protocols differ between studies and have changed with time, and details of test kits used at each site since 1990 have been published.(217-222) HIV testing was done in the home, except in Kisesa, where serological surveillance was done in specially constructed temporary village clinics, to which people were transported by project vehicles from their homes. Before 2003, all studies (excluding Karonga) followed a research test protocol of informed consent without disclosure (in uMkhanyakude, participants received detailed verbal and written pretest information), but as antiretroviral therapy (ART) became available, testing protocols that offer, but do not insist upon, full pretest and post-test counselling were gradually adopted. Karonga had always offered full pretest and post-test counselling.

Procedures

A common format and coding system were agreed with the six African study sites for all data variables used in the analyses. After a series of analysis workshops, each study contributed a data set meeting the agreed specification, and the data were pooled by analysts at the London School of Hygiene & Tropical Medicine (London, UK). Data management programs were developed in Stata (version 12) to clean the pooled data set, so that all data met the same validity and consistency criteria for statistical analysis. The data cleaning programs and the subsequent statistical analyses programs were made available to the study sites for further use with their own data. Analyses presented in this Article relate to all deaths occurring in pregnant or postpartum women (up to 42 days postpartum). We did not exclude causes that are incidental to pregnancy, and thus we use the term pregnancy-related mortality rather than maternal mortality to describe our findings.

Verbal autopsy interviews are structured interviews with persons who cared for or were close to the deceased during the final illness, and can report signs and symptoms that they noted during this period.(24) Interviews were triggered by reports of deaths collected during demographic surveillance at all sites except Manicaland and Masaka, where community-based informants were used. At Masaka, the deaths for which verbal autopsy interviews were done occurred between March, 1990, and November, 1992, or

between January, 2006, and November, 2008; data were gathered continuously at all other sites. Instruments for verbal autopsies were developed largely independently by each study, with convergence to compatibility with international standards by 2011.(223, 224) We used only two sets of responses in this analysis—those to questions about whether the woman was pregnant or postpartum when she died and whether she had ever tested positive for HIV infection.

In accordance with the tenth revision of the International Classification of Diseases,(102) we classified death as pregnancy-related if it occurred while the woman was pregnant or postpartum, irrespective of the cause of death. Pregnancy or birth reports that identified a death as pregnancy-related were obtained either from demographic surveillance or from verbal autopsies.

Statistical analysis

Person-time at risk of a pregnancy-related death was calculated. For births recorded by demographic surveillance, 280 days of pregnancy (unless curtailed by the woman arriving in the study area after the start of her pregnancy) and 42 days postpartum exposure (unless curtailed by the woman's death or departure from the study area) were assumed for calculations of person-time at risk of pregnancy-related death. When pregnancy was recorded (either by demographic surveillance or verbal autopsy) but no birth report obtained (because the woman died or left the study area before delivery), we assumed that the pregnancy report was made on day 185 of the pregnancy—i.e., halfway between day 90 and day 280—on the grounds that pregnancies would be unlikely to be recognised and reported before the first trimester.

In our analysis, women have a risk of dying or giving birth as soon as they turn 15 years old and have been listed as members of a study household during demographic surveillance. The risk period ends when they are aged 50 years or older or leave the study area through death or migration.

Person-time is classified as HIV-uninfected from the first HIV-negative test date to a predetermined period after the last HIV-negative test. For women who subsequently test positive for HIV infection, the remaining HIV-uninfected period is half the interval between the last negative test and the first positive test. For women who do not test positive after their last HIV-negative test, the remaining HIV-uninfected period was defined as 5 years for Karonga, Kisesa, Masaka, and Rakai, 3 years for Manicaland, and 1.5 years for uMmkhanyakude. These periods roughly correspond to the time that

it would take for 5% of HIV-uninfected women at the different study sites to seroconvert.

Person-time after the first HIV-positive test was classified as HIV-infected, as was half the person-time in a seroconversion period. Verbal autopsies might identify HIV-infected women who had not tested positive in a serosurvey, such as women who were tested before moving to the study area or tested outside the research setting (e.g., at an antenatal clinic) and subsequently did not take part in research tests. To avoid counting these deaths without allocation of an appropriate amount of person-time at risk, we assumed that women who were established to be HIV-infected on the basis of verbal autopsies had been infected for 5 years – i.e., half the median post-infection survival time in the pooled data set.(97)

We classified person-time for women who were never tested and person-time lived outside that classified as HIV-infected or HIV-uninfected as HIV status unknown. We divided exposure years into calendar time before ART was available, during ART rollout, and after widespread ART availability in health facilities serving each study.

The period prevalence of HIV infection was calculated by dividing the HIV-infected person-years by the sum of the years of known HIV status. We estimated the general fertility rate as the total number of births divided by the total number of person-years to women of reproductive age.

We calculated mortality rates per 1,000 person-years by pregnancy and HIV status, and used the age distribution of all women as a standard to calculate age-standardised mortality. The rate ratio was calculated by dividing the mortality rate in HIV-infected women by that in HIV-uninfected women for pregnant or postpartum women and for those who were not pregnant or postpartum. For the pooled data set, we used Mantel-Haenszel estimates to calculate an age-adjusted rate ratio, but could not calculate age-adjusted rate ratios for each site because of small numbers.

To quantify the excess risk of mortality in HIV-infected women, the attributable rate was calculated as the mortality rate in HIV-infected women minus that in HIV-uninfected women. We divided the attributable rate by the mortality rate in HIV-infected women to calculate the attributable rate percentage of deaths due to HIV infection. To assess the effect of HIV on mortality at the population level, we calculated the population-attributable rate – i.e., the mortality rate in all women minus that in HIV-uninfected

women. We then divided the population-attributable rate by the mortality rate in all women to give the population-attributable fraction (PAF). To predict PAFs in pregnant women in populations with known prevalences of HIV infection on the basis of noted rate ratios of mortality of HIV-infected to HIV-uninfected pregnant or postpartum women in the pooled ALPHA data set, we used the standard relation:(88)

$$PAF = \frac{prevalence\ x\ (rate\ ratio - 1)}{1 + prevalence\ x\ (rate\ ratio - 1)}$$

6.2.4 Results

Table 6.1 lists the six independently established studies that contributed data for our analysis. 138,074 women aged 15–49 years contributed 636,213 person-years of observation between June, 1989, and April, 2012. HIV status was known for 321,817 of 636,213 (50.6%) person-years (Table 6.2). 49,568 women had 86,963 pregnancies; HIV status was known during 49,740 (57.2%) of these pregnancies. 6,760 deaths were reported in women of reproductive age, of which 3,709 (54.9%) could be classified by HIV status (Table 6.2). Of the 235 of these deaths that were in women who were pregnant or postpartum, HIV status was known for 118 (50.2%; Table 6.2).

Table 6.1: Characteristics of ALPHA study sites contributing data for HIV and pregnancy-related mortality

	London School of Hygiene and Tropical Medicine	National Institute of Medical Research, Tanzama	Imperial College and Biomedical Research Training Institute	Uganda Virus Research Institute and UK Medical Research Council	Mankerere University and Johns Hopkins School of Public Health	Africa Centre and University of KwaZulu-Natal
Location	Karonga, Malawi	Kisesa, Tanzania	Manicaland, Zimbabwe	Masaka, Uganda	Rakai, Uganda	uMkhanyakude, South Africa
Dates for which HIV data are available	2005-12	1994-2011	1994-2008	1989-2011	1994-2009	2003-11
Prevalence of HIV infection at start date[1]	12%	5%	24%	7%	16%	22%
Prevalence of HIV infection at start date[1]	8%	6%	14%	9%	11%	29%
Population at start date (n)[2]	31,000	20,000	15,000	8,000	30,000	93,000
Population at end date (n)[2]	35,000	34,000	37,000	19,000	40,000	96,000
Frequency of DSS data collection	Continuous (through key informants)	Every 6 months	Every 2-3 years	Every year	Every 14-16 months	Every 6 months
Frequency of HIV data collection	Variable (< every 3 years)	Every 3 years	Every 2-3 years	Every year	Every 14-16 months	Every year

Collection periods for verbal autopsy data	2003-2012	1994-2011	1994-2008	1990-92, 2006-08	1996-2009	2003-11
Period of roll-out of ART	2005-06	2005-08	2007-09	2004-05	2004-06	2004-06

Abbreviations: ART=antiretroviral therapy, DSS=demographic surveillance site
[1]In people aged 15 or older
[2]Populations are rough estimates; numbers are rounder for ease of comparison

Table 6.2: Mortality in pooled ALPHA network data by pregnancy and HIV status, 1990-2012

	Deaths	Person-years[1]	Mortality per 1,000 person-years (95% CI)	Age standardised mortality per 1,000 personyears
Not pregnant and more than 42 days postpartum				
Known HIV status	3591	282,664	12.7 (12.3-13.1)	12.8 (12.4-13.2)
HIV-uninfected	652	231,804	2.8 (2.6-3.0)	2.8 (2.6-3.0)
HIV-infected	2939	50,859	57.8 (55.7-59.9)	57.6 (55.5-59.6)
Unknown HIV status	2934	284,960	10.3 (9.9-10.7)	10.3 (9.9-10.7)
Total	6525	567,624	11.5 (11.2-11.8)	11.5 (11.3-11.8)
Pregnant or up to 42 days postpartum				
Known HIV status	118	39,153	3.0 (2.5-3.6)	3.6 (2.3-5.0)
HIV-uninfected	58	34,774	1.7 (1.3-2.2)	2.4 (1.0-3.8)
HIV-infected	60	4,380	13.7 (10.6-17.6)	16.1 (10.3-21.9)
Unknown HIV status	117	29,436	4.0 (3.3-4.8)	5.2 (3.0-7.3)
Total	235	68,590	3.4 (3.0-3.9)	4.3 (3.1-5.5)
All women of reproductive age				
Known HIV status	3709	321,817	11.5 (11.2-11.9)	-
HIV-uninfected	710	266,578	2.7 (2.5-2.9)	-
HIV-infected	2999	55,240	54.3 (52.4-56.3)	-
Unknown HIV status	3051	314,396	9.7 (9.4-10.1)	-
Total	6760	636,213	10.6 (10.4-10.9)	-

Abbreviations: CI=confidence interval
[1]Data in the person-years column might not add exactly due to rounding

The overall mean prevalence of HIV infection during the data collection period in the pooled data set was 17.2% (95% CI 17.0–17.3). Prevalence in pregnant or postpartum women (11.2%, 95% CI: 10.9–11.5) was significantly lower than that in women who were not pregnant or postpartum (18.0%, 95% CI: 17.9–18.1, p<0.0001). Figure 6.1 shows the prevalence of HIV infection in women of reproductive age by year.

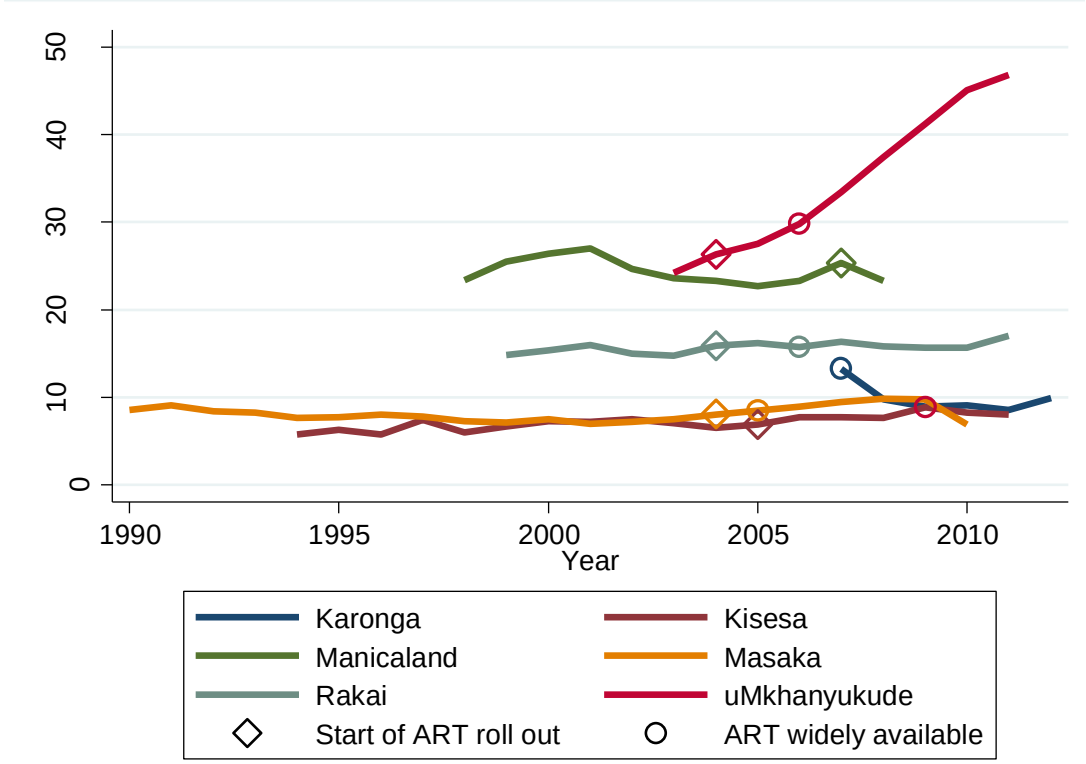

Figure 6.1. Calender-year time trends in the HIV prevalence amongst women of repoductive age by study site

Mean prevalence was 7.2% (95% CI: 7.0–7.4) in Kisesa, 8.2% (95% CI: 7.9–8.4) in Masaka, 9.6% (95% CI: 9.2–10.0) in Karonga, 15.7% (95% CI: 15.5–15.9) in Rakai, 24.5% (95% CI: 24.0–25.0) in Manicaland, and 35.4% (95% CI: 35.0–35.8) in uMkhanyakude. Mean prevalence in women who were pregnant or postpartum was significantly lower than that in women who were not pregnant or postpartum (data not shown).

The general fertility rate in the pooled data set was 132 (95% CI: 131–133) births per 1,000 person-years. Fertility rates were significantly lower in HIV-infected women (100, 95% CI: 97–104) than in HIV-uninfected women (172, 95% CI: 170–174, p<0.0001). General fertility rates were lower in the southern African sites—ie, Manicaland (85.8, 95% CI: 82.5–89.1) and uMkhanyakude (98.2, 95% CI: 96.9–99.5)—than in the east African sites—ie, Karonga (190.5, 95% CI: 187.1–194.0), Kisesa (180.6, 95% CI: 177.9–183.4), Masaka (157.9, 95% CI: 154.7–161.2), and Rakai (125.1, 95% CI: 123.3–126.9). Mortality in HIV-uninfected women was 1.5 (95% CI: 1.1–1.9) per 1,000 person-years at uMkhanyakude, which was lower than that at the other sites combined (2.9, 95% CI: 0.27–0.31 per 1,000 person-years).

Table 6.3 shows the distribution of deaths at each site classified by HIV status and whether or not women were pregnant or postpartum. The uMkhanyakude site contributed 29.3% of all the deaths in women of known HIV status, 22.9% of the pregnancy-related deaths in women of known HIV status, and 34.3% of all deaths in HIV-infected women (Table 6.3).

Table 6.3: Deaths in women aged 15-49 years by study site and HIV status

	Karonga	Kisesa	Manicaland	Masaka	Rakai	uMkhanyakude	Total
Pregnancy-related deaths							
HIV uninfected	7/42 (17%)	30/62 (48%)	7/23 (30%)	7/13 (54%)	4/20 (20%)	3/75 (4%)	58/235 (25%)
HIV infected	5/42 (12%)	7/62 (11%)	15/23 (65%)	3/13 (23%)	6/20 (30%)	24/75 (32%)	60/235 (26%)
Unknown	30/42 (71%)	25/62 (40%)	1/23 (4%)	3/13 (23%)	10/20 (50%)	48/75 (64%)	117/235 (50%)
All other deaths							
HIV uninfected	25/321 (8%)	127/545 (23%)	199/806 (25%)	110/580 (19%)	135 /1468 (9%)	56/2805 (2%)	652/6525 (10%)
HIV infected	110/321 (34%)	159/545 (29%)	588/806 (73%)	305/580 (53%)	772/1468 (53%)	1005/2805 (36%)	2939/6525 (45%)
Unknown	186/321 (58%)	259/545 (48%)	19/806 (2%)	165/580 (28%)	561/1468 (38%)	1744/2805 (62%)	2934/6525 (45%)

Of the 235 pregnancy-related deaths, 40 (17.0%) were identified as pregnancy-related by both verbal autopsy data and demographic surveillance data, 144 (61.3%) were identified as pregnancy-related on the basis of verbal autopsy reports alone, and the remaining 51 (21.7%) were identified through demographic surveillance only. In this last group of 51, verbal autopsy was not done in 24 cases and did not directly identify the death as pregnancy-related in 27 cases. The study with the lowest proportion of pregnancy-related deaths with verbal autopsy data was Masaka (23.1%). Rakai relied exclusively on verbal autopsies to identify pregnancy-related deaths. In Kisesa and Manicaland, less than 20% of the pregnancy-related deaths were identified as such via demographic surveillance system (data not shown).

Overall mortality in the pooled data set was 10.6 (95% CI: 10.4–10.9) per 1,000 person-years. In HIV-infected women, overall mortality was 54.3 (95% CI: 52.4–56.3) per 1,000 person-years compared with 2.7 (95% CI: 2.5–2.9) in HIV-uninfected women. It was 9.7 (95% CI: 9.4–10.1) per 1,000 person-years in women of unknown HIV status, which was lower than the mean mortality of women with known HIV status (11.5, 95% CI: 11.2–11.9 per 1,000 person-years). 49.2% of the person-years of

unknown HIV status were contributed by the uMkhanyakude site, where participation rates in HIV surveillance were lower than at other sites (data not shown).

Table 6.2 shows deaths, person-years of exposure, and resulting mortality by pregnancy or postpartum status and HIV status. 60 of 118 (50.8%) pregnant or postpartum women of known HIV status who died were infected with HIV (Table 6.2). Figure 6.2 contains further breakdown of these results by study site.

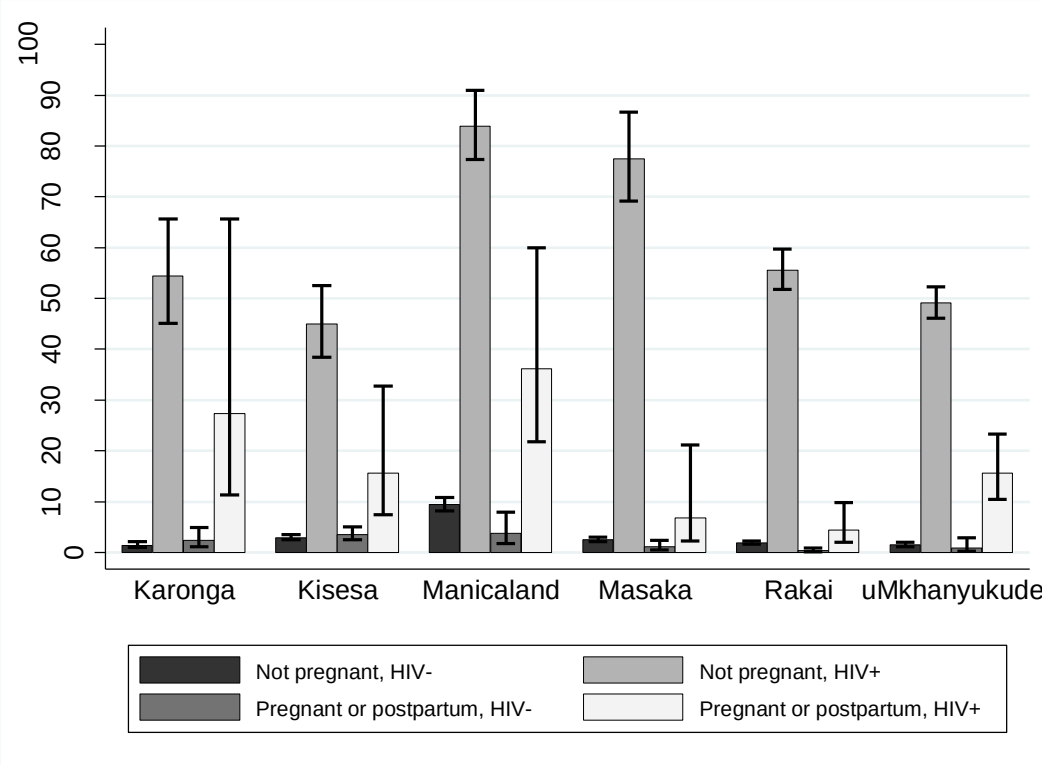

Figure 6.2: Mortality rates in HIV-infected and uninfected women by pregnancy status and study site

During the study period, HIV-infected women had much higher mortality than had uninfected women. The crude rate ratio of mortality in HIV-infected women who were not pregnant or postpartum to that in HIV-uninfected women who were not pregnant or postpartum was 20.5 (95% CI: 18.9–22.4); in pregnant or postpartum women, the corresponding rate ratio is 8.2 (95% CI: 5.7–11.8; Table 6.4). After adjustment for age, the rate ratio for women who were not pregnant or postpartum fell to 19.0 (95% CI: 17.3–20.8) and that for pregnant or postpartum women increased slightly to 9.0 (95% CI: 6.1–13.1). Mortality rate ratios varied substantially across study sites (Table 6.4). At all sites, the rate ratios were substantially higher in women who were not pregnant or postpartum than in those who were pregnant or postpartum, with the exception of Manicaland, where the ratios were very similar in the two groups (Table 6.4). Sensitivity

analyses showed little effect on the crude rate ratio of varying the assumptions around the person-time allocated as HIV-infected before death for HIV infection reported in verbal autopsies, or HIV uninfected time after a last HIV negative test (described in detail in Section 6.3.1).

Table 6.4: Crude rate ratio of mortality rates in HIV-infected and HIV-uninfected women and population attributable fractions for HIV, by study site

	Crude rate ratio (95% CI)		Population attributable fraction (95% CI)	
	Pregnant or postpartum	Not pregnant or postpartum	Pregnant or postpartum	Not pregnant or postpartum
Karonga	11.7 (3.7-37.0)	38.7 (25.1-59.7)	38.0	79.3
Kisesa	4.4 (1.9-10·1)	15.2 (12.1-19.2)	14.6	51.7
Manicaland	9·5 (3·9-23·4)	8.9 (7.5-10.4)	60.8	65.7
Masaka	5.9 (1.5-22.9)	30.5 (24.5-37.9)	24.9	70.9
Rakai	13.4 (3.8-47.4)	28.7 (23.9-34.5)	55.5	82.0
uMkhanyukude	16.8 (5.1-55.9)	32.4 (24.7-42.3)	83.5	91.7
All sites	8.2 (5.7-11.8)	20.5 (18.9-22.4)	44.6	77.6

Abbreviations: CI=confidence interval

Figure 6.3 shows the mortality rates for women with known HIV status, broken down by availability of ART. Mortality fell substantially in HIV-infected women who were not pregnant or postpartum; the mortality rate ratio comparing the post-ART period with the pre-ART period was 0.42 (p<0.0001). In woman who were pregnant or postpartum, the fall was much smaller (0.70 [p=0.205]).

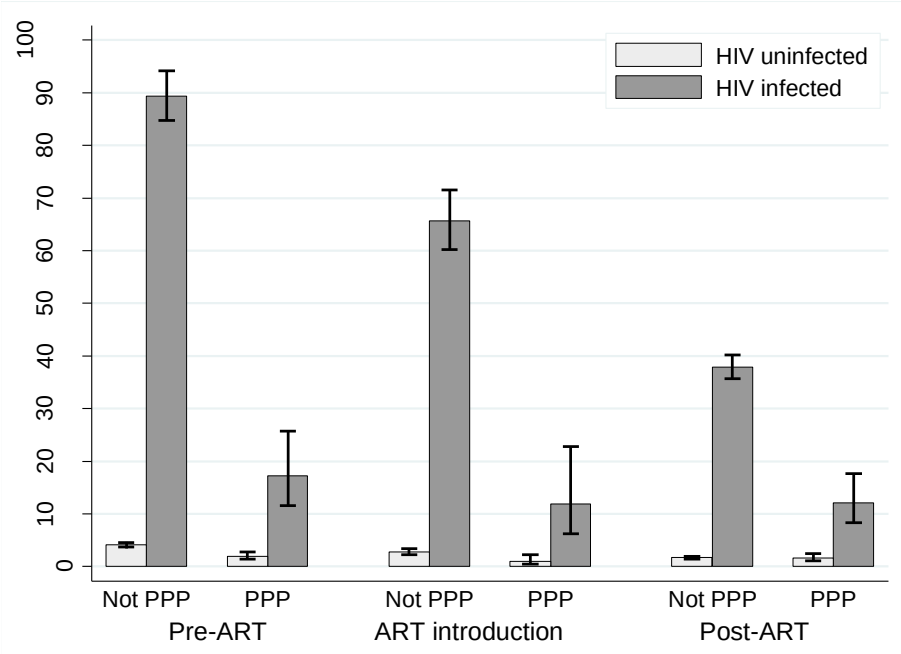

Figure 6.3: Mortality rates in HIV-infected and HIV-uninfected women, by pregnancy status and availability of ART. Bars are 95% confidence intervals. Abbreviations: ART=Antiretroviral therapy, PPP=pregnant or postpartum

Figure 6.4 compares, for each study, the proportion of pregnant or postpartum women infected with HIV at the time of their death, with the mean prevalence of HIV infection in the child-bearing population during the study period. The relation was not linear, but prevalence of HIV infection in living pregnant or postpartum women (range 7–35) was associated with that in pregnant or postpartum women who died (19–89). Prevalence of HIV infection in pregnant or postpartum women who died was between 2.5 and 4.5 times that in living women aged 15–50 years.

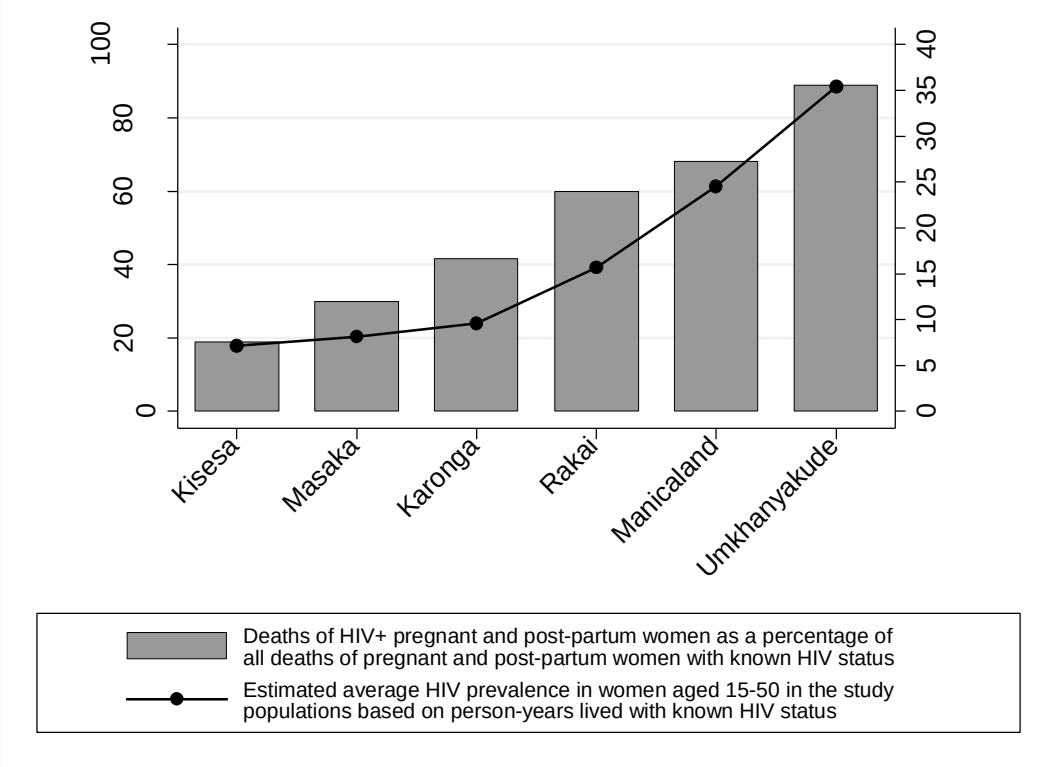

Figure 6.4: Proportion of pregnant or postpartum women infected with HIV at the time of their deaths amongst all deaths of pregnant or postpartum women with known HIV status, and mean prevalence of HIV infection amongst women of reproductive age, by study site. Abbreviations: PPP=pregnant or postpartum

6.2.5 Discussion

In the pooled ALPHA data, HIV-infected pregnant or postpartum women had an eight-times higher risk of dying than did HIV-uninfected counterparts. In women who were not pregnant or postpartum, the risk in HIV-infected women was slightly more than 20 times that in HIV-uninfected women. Excess mortality attributable to HIV was substantially lower in HIV-infected pregnant or postpartum women than that in HIV-infected women who were not pregnant or postpartum. Thus, the HIV PAF is much

smaller for pregnant or postpartum women than for women who were not pregnant or postpartum (78%).

Lower excess mortality attributable to HIV in HIV-infected pregnant or postpartum women than in HIV-infected women who are not pregnant or postpartum is perhaps not surprising. Although HIV has been classified by some analysts as an indirect cause of maternal death(29)—implying that HIV disease progression is aggravated by pregnancy—evidence for the adverse effect of pregnancy on HIV progression and mortality in HIV-infected women is weak.(101) Excess mortality might be counter-balanced by the fact that fertility falls rapidly with duration of HIV infection(225) and with age, whereas mortality increases with age and rises very rapidly with duration of HIV infection. When women are ill with AIDS or an AIDS-related disorder, they are unlikely to become pregnant and are thus unlikely to die while pregnant or postpartum. This so-called healthy pregnant women effect—a selection effect whereby healthier women are the ones who become pregnant—has been described in other settings (where it is mainly due to the younger age of pregnant women relative to non-pregnant women), but is more strongly apparent when HIV is the main cause of death in adults.(124)

Provision of services to prevent mother-to-child transmission of HIV probably did not confer health advantages to the pregnant women in this study. Most of the data (roughly 64%) relating to the mortality exposure of pregnant women were gathered before such services were widely available at the study sites. The drugs given in the early programmes to prevent mother-to-child transmission were one-off doses close to the time of delivery (too late to affect survival for most of the at-risk period). The aim was to decrease the probability of transmission to the neonate rather than to improve the mother's survival chances. WHO's 2010 guidelines(174) include recommendations for ART aimed at improvement of survival of mothers, but these guidelines had not yet been implemented at any of the study sites during the study, and by 2011–12, pregnant or postpartum women had not benefited significantly from ART availability, unlike their non-pregnant counterparts.

The PAF of 44.6% corresponded to an overall mean prevalence of HIV infection of 17.2% in the ALPHA surveillance populations; the crude rate ratio in the pooled data set was 8.2. On the basis of the standard relations between PAF, prevalence, and rate ratio, we expected a PAF for HIV of around 24% in pregnancy-related mortality for sub-Saharan Africa, where the Joint UN Programme on HIV/AIDS (UNAIDS) estimate that

the 2010 prevalence of HIV infection in pregnant women is 4.4% (unpublished).(226) The results of a systematic review showed that an estimated 25% of pregnancy-related deaths were attributable to HIV in sub-Saharan Africa.(98) Globally, the equivalent estimate for the proportion of pregnancy-related deaths attributable to HIV is roughly 8%, which is based on the (unpublished) UNAIDS global estimate of 1.2% prevalence of HIV infection in pregnant women.(226) We would expect the proportion of maternal mortality attributable to HIV to be less than this estimate if some of the AIDS deaths in pregnant or postpartum women are classified as incidental to pregnancy.

Modelled estimates for the proportion of maternal mortality attributable to HIV in sub-Saharan Africa range from 10% to 32%.(17, 32) However, confidential inquiries in South Africa suggest that roughly 70% of pregnant or postpartum women who die in hospital might be HIV-infected,(210, 227) and estimates based on these data suggest a PAF for HIV of about 58%. In the pooled ALPHA data set, 51% of the pregnant or postpartum women who died were infected with HIV. The standard relations between PAF, prevalence, and rate ratio led us to expect a PAF for HIV of 56% in South African institutional pregnancy-related deaths—very close to the noted figure.

The overall ratio of pregnancy-related deaths to pregnancies for all sites was 270 per 100,000 pregnancies—1,015 per 100,000 in HIV-infected women and 119 per 100,000 in HIV-uninfected women. In view of the fact that women in sub-Saharan Africa have very low access to high-quality obstetric care, these ratios are low and generally fall below the modelled maternal mortality estimates for sub-Saharan Africa in 1990–2010 published by WHO (850-500 maternal deaths per 100,000 live births)(32) and the Institute for Health Metrics and Evaluation (490-170 maternal deaths per 100,000 live births).(29) However, the ratios in the ALPHA data set (1015 per 100,000 for HIV-infected women, 270 per 100,000 for HIV-uninfected women) were higher than institutional ratios for pregnancy-related deaths reported in South Africa (430 per 100,000 for HIV-infected women, 75 per 100,000 for HIV-uninfected women).(210) HIV ascertainment was not related to the ascertainment of pregnancy, so the probable underestimation of pregnancy-related deaths should not affect the rate ratio comparisons of pregnancy-related mortality in HIV-infected and HIV-uninfected women.

Our study has several limitations. Even after pooling of the data from all six studies we identified only 235 pregnancy-related deaths. Compared with studies designed to track maternal deaths by frequent checks on pregnancy status and close surveillance of pregnant women, the ALPHA community studies, which were designed for HIV

surveillance, did not detect all pregnancy-related deaths. Several factors might contribute to this failure to detect pregnancy-related deaths. Pregnancies might not be reported because women are embarrassed or because of proxy reporting by other household members. Furthermore, studies that undertake demographic surveillance with intervals longer than six months would not intersect with all the times during which women would recognise that they were pregnant.

Verbal autopsy seems a more reliable way to identify pregnancy-related deaths than is the demographic surveillance system, and thus, because 1868 (27.6%) of all deaths in the pooled data set did not have an associated verbal autopsy, we might have missed some pregnancy-related deaths. 184 of 4892 (3.8%) deaths for which verbal autopsies were done seemed to be pregnancy-related, whereas only 24 of 1868 (1.3%) of those for which verbal autopsies were not done were identified as pregnancy-related from the demographic surveillance system. On the basis of typical capture–recapture assumptions (i.e., that the likelihood of a death being related to pregnancy is independent of acquisition of verbal autopsy data), we estimate that universal coverage of verbal autopsies could have identified about 50 more pregnancy-related deaths, implying an overall underestimate of roughly 18% in the number of pregnancy-related deaths. However, this underestimate is unlikely to be related to HIV status, because we noted no signs of a relation between verbal autopsy and HIV ascertainment.

Inter-study variation in the frequency of serological surveillance and prevalence of HIV infection meant that varying numbers of person-years after the last HIV-negative test were censored by transferring individuals to the unknown HIV status category, ranging from 1.5 years in uMkhanyakude to 5 years in Karonga, Kisesa, Masaka, and Rakai. The sensitivity analysis in Section 6.3.1 shows that the effect of our assumptions on the mortality rate ratios of pregnant or postpartum women was insignificant. Similarly, the sensitivity analysis for the length of time spent infected with HIV by women who were identified as being infected only by verbal autopsy shows that estimates of mortality rate ratios were not affected.

HIV status was more likely to be missing for women who died than for women in general, and in all studies, death rates in women with unknown HIV status were higher than those in women whose HIV status was known, suggesting that the prevalence of HIV infection in women whose HIV status was known underestimated overall prevalence. A crude application of the mortality-rate-adjustment method for estimation of recorded prevalence of HIV infection allowing for under-reporting (which was

developed in the Africa Centre)(228) suggested that the overall mean prevalence of HIV infection might have been underestimated by as much as 30% in the pooled data set—partly a result of the high prevalence in data from the Africa Centre, which also has the highest proportion of women with unknown HIV status. Higher prevalence of HIV infection in each contributing study would raise the PAF of deaths due to HIV in all women, but especially in those who were not pregnant or postpartum.

Our results show that, in populations with a high prevalence of HIV infection, a very high proportion of deaths during pregnancy or the postpartum period were attributable to HIV. HIV and reproductive health services need to be integrated with safe motherhood programmes, and the focus of safe motherhood campaigns should be extended beyond direct obstetric causes of death. Many national HIV control programmes are widening access to ART. In 2013, South Africa will enable all HIV-infected pregnant women to receive treatment from early pregnancy throughout the duration of breastfeeding, and other countries, such as Malawi, are already providing all HIV-infected pregnant women with lifelong ART. Such wider eligibility criteria should cause HIV-related deaths in women of childbearing age to decline rapidly if safe motherhood programmes ensure that pregnant women discovered to be infected with HIV are actively encouraged to take up ART, over and above the routine advice that is provided about prevention of HIV transmission to the unborn child.

6.3 SUPPLEMENTARY MATERIAL: TESTING THE SENSITIVITY OF THE PUBLISHED RESULTS

This section will summarise three sets of analyses which were undertaken to test the sensitivity of the results which were included in the published article. These sensitivity analyses will explore the effect of:

1. Varying the definition of HIV status
2. Varying the definition of pregnancy status
3. Adjusting for multiple covariates

6.3.1 Varying the definition of HIV status

A number of sensitivity analyses were undertaken to explore the effect of our definition of HIV status on the ratio of the mortality rates in HIV-infected women to those of uninfected women.

Post-negative time

Assumptions were made about how long to assume individuals remained HIV negative after observing an HIV negative test result which was not followed by a positive test result. This was set to approximate the number of years it would take for 5% of the cohort to seroconvert: five years for Kisesa, Karonga, Rakai and Masaka; three years for Manicaland and; one and a half years for uMkhanyakude.

Figure 6.5 shows how the rate ratio varies by proportional changes to the post-negative assumptions. Assuming the post-negative time to be 20% less for each site results in small increases in the rate ratio from 20.5 (95% CI: 18.9-22.4) up to 22.5 for non-pregnant or postpartum women (95% CI: 20.6-24.6), but similar increases were not observed for pregnancy-related mortality. Doubling the post-negative time resulted in decreases in the rate ratio for the non-pregnant and postpartum women to 18.2 (95% CI: 16.8-19.7) and from 8.2 (95% CI: 5.7-11.8) to 7.6 (95% CI: 5.3-10.8) for pregnant and postpartum women.

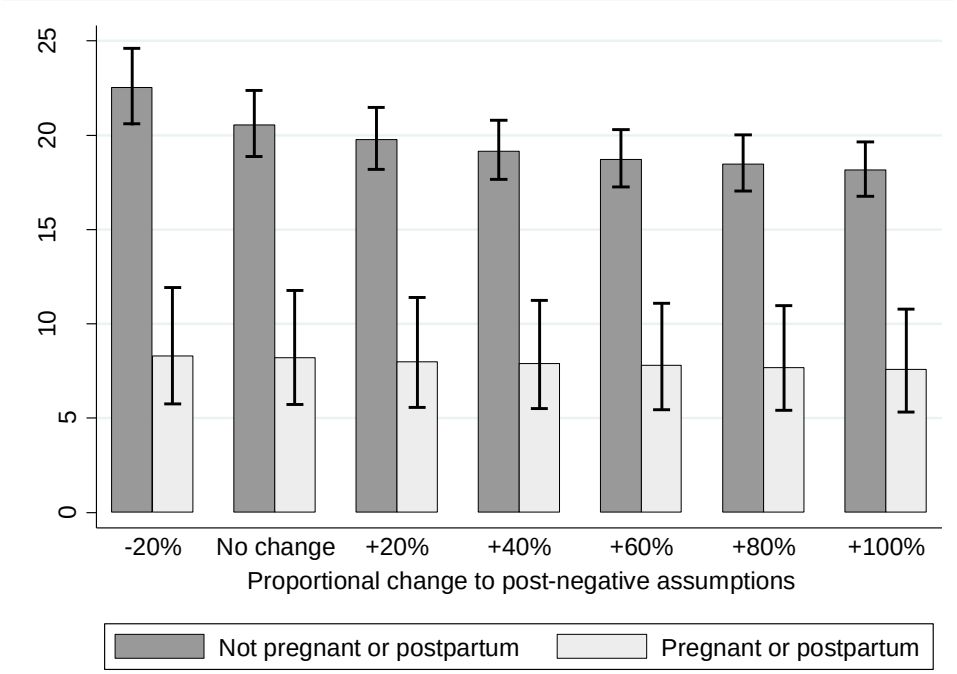

Figure 6.5: Effect of varying the post-negative HIV test assumption proportionally on the rate ratio comparing mortality in HIV-infected and HIV-uninfected women by pregnancy status

Pre-positive time

For those who were identified as HIV-infected based on HIV serosurveys, time as HIV-infected was only classified as HIV-infected from the date of the first HIV positive test result. Figure 6.6 shows rate ratio comparing mortality in HIV-infected women to that in HIV-uninfected women for varying numbers of years classified as HIV-infected before the first HIV positive test result. Declines in the rate ratio are seen in both pregnant/postpartum women and the non-pregnant women; although the rates in HIV-infected women always remain significantly higher than amongst HIV-uninfected women.

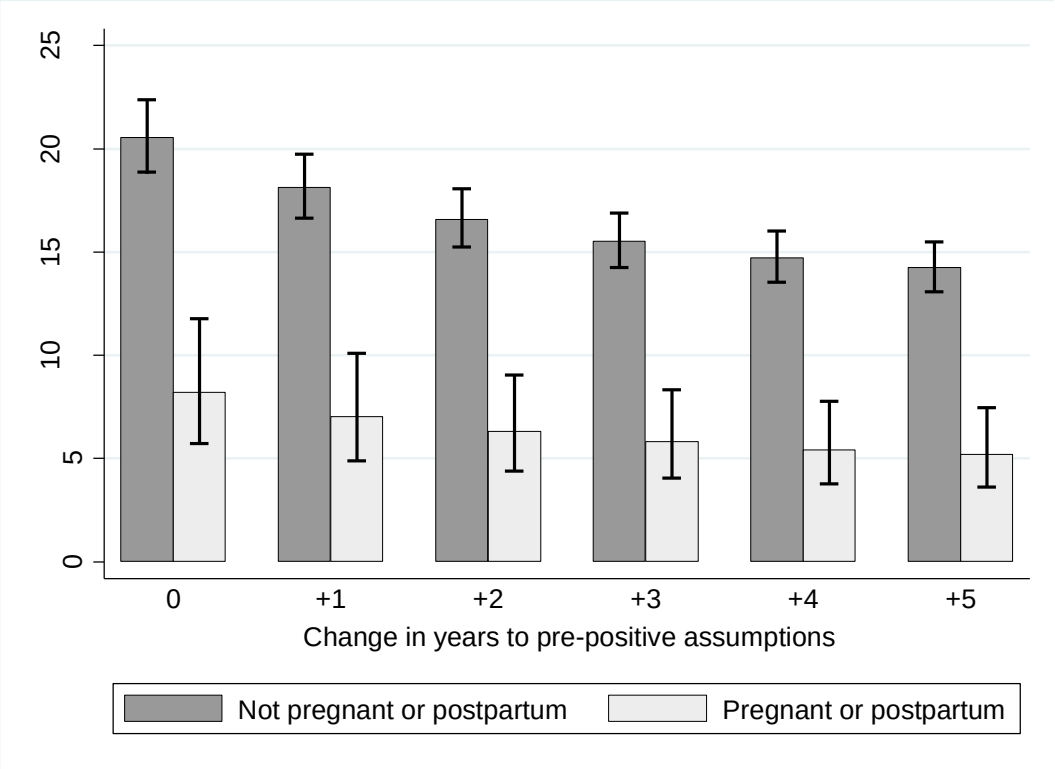

Figure 6.6: Effect of varying the pre-positive HIV test assumption absolutely on the rate ratio comparing mortality in HIV-infected and HIV-uninfected women by pregnancy status

For those who were identified as HIV-infected based on reports from the verbal autopsy (VA), five years before the date of death were assumed to be spent HIV-infected. Figure 6.7 shows that varying this assumption results in no change to the rate ratios in the published paper. This is unsurprising as only seven deaths not identified as HIV-infected through serosurveys were identified as HIV-infected through VA reports.

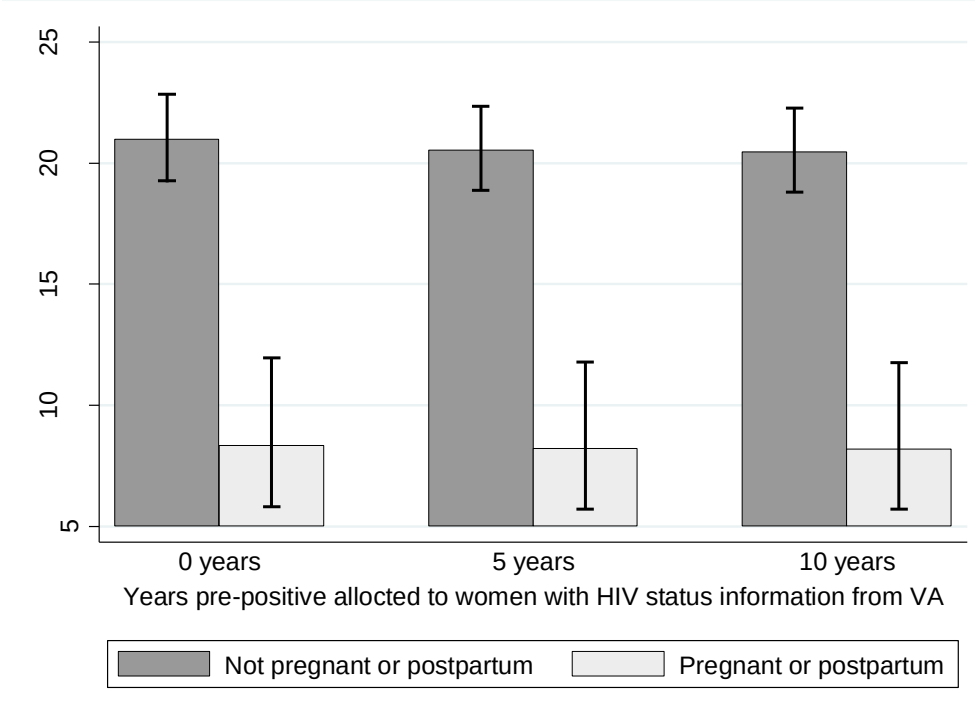

Figure 6.7: Effect of varying the pre-positive HIV test assumption for those who had the positive status assigned from the verbal autopsy on the rate ratio comparing mortality in the HIV-infected and HIV-uninfected women by pregnancy status.

6.3.2 Varying the postpartum length of follow-up

Changing the definition of "pregnant or postpartum" to include women up to one year postpartum rather than just 42 days postpartum, increased to 11.4 (95% CI: 8.8-14.8) the rate ratio comparing pregnancy-related mortality rates in HIV-infected women to those in uninfected women. The equivalent rate ratio for women who are neither pregnant nor up to one year postpartum falls to 19.9 (95% CI: 18.2-21.7) (Table 6.5). Table 6.5 also shows these rate ratios when the postpartum period at risk is assumed to last up to two years.

Table 6.5: Crude rate ratio of mortality rates in HIV-infected and HIV-uninfected women and population attributable fractions for HIV, by varying lengths of postpartum follow-up

	HIV status	Number of deaths	Person-years	Mortality per 1,000 person-years (95% CI)	Mortality rate ratio (95% CI)	Population attributable fraction
42 days						
Pregnant or up to 42 days postpartum	**HIV-uninfected**	58	34,774	1.7 (1.3-2.2)	1	-
	HIV-infected	60	4,380	13.7 (10.6-17.6)	8.2 (5.7-11.8)	44.6
Not pregnant or up to 42 days postpartum	**HIV-uninfected**	652	231,804	2.8 (2.6-3.0)	1	-
	HIV-infected	2,939	50,859	57.8 (55.7-59.9)	20.5 (18.9-22.4)	77.6
1 year						
Pregnant or up to one year postpartum	**HIV-uninfected**	97	71251	1.4 (1.1-1.7)	1	-
	HIV-infected	148	9518	15.6 (13.2-18.3)	11.4 (8.8-14.8)	55.0
Not pregnant or up to one year postpartum	**HIV-uninfected**	613	195327	3.1 (2.9-3.4)	1	-
	HIV-infected	2,851	45722	62.4 (60.1-64.7)	19.9 (18.2-21.7)	77.9
2 years						
Pregnant or up to two years postpartum	**HIV-uninfected**	174	103,004	1.7 (1.5-2.0)	1	-
	HIV-infected	334	14,876	22.5 (20.2-25.0)	13.3 (11.1-16.0)	60.7
Not pregnant or up to two years postpartum	**HIV-uninfected**	536	163,574	3.3 (3.0-3.6)	1	
	HIV-infected	2,665	40,364	66.0 (63.6-68.6)	20.1 (18.4-22.1)	75.4

Abbreviations: CI=confidence interval

6.3.3 Adjusting for multiple covariates

Poisson regression was undertaken to explore the effect of adjusting simultaneously for age and study site on the association between HIV and mortality. For pregnant and postpartum women, the rate ratio comparing mortality rates in HIV-infected women to uninfected women increased slightly to 8.6 (95% CI: 5.8-12.7) after adjusting for age and study (Table 6.6).

Table 6.6: Mortality rates ratios from a Poisson regression model for pregnant and postpartum women

	Number of deaths	Person-years	Mortality per 1,000 person-years (95% CI)	Crude mortality rate ratio (95% CI)	Adjusted mortality rate ratio (95% CI)[1]
HIV status					
HIV-uninfected	58	34,774	1.7 (1.3-2.2)	1	1
HIV-infected	60	4,380	13.7 (10.6-17.6)	8.2 (5.7-11.8)	8.6 (5.8-12.7)
Age group					
15-29	70	27,247	2.6 (2.0-3.3)	1	1
30-39	37	10,437	3.6 (2.6-4.9)	1.4 (0.9-2.1)	1.1 (0.8-1.7)
40-49	11	1,470	7.5 (4.2-13.5)	2.9 (1.5-5.5)	2.8 (1.5-5.3)
Site name					
Karonga	12	3,189	3.8 (2.1-6.6)	1	1
Kisesa	37	8,954	4.1 (3.0-5.7)	1.1 (0.6-2.1)	1.1 (0.6-2.1)
Manicaland	22	2,259	9.7 (6.4-14.8)	2.6 (1.3-5.2)	1.6 (0.8-3.2)
Masaka	10	6,502	1.5 (0.8-2.9)	0.4 (0.2-1.0)	0.4 (0.2-0.9)
Rakai	10	13,482	0.7 (0.4-1.4)	0.2 (0.1-0.5)	0.2 (0.1-0.4)
uMkhanyakude	27	4,768	5.7 (3.9-8.3)	1.5 (0.8-3.0)	0.6 (0.3-1.3)

Abbreviations: CI=confidence interval
[1]Adjusted for: HIV status, age group and site name

For women who were neither pregnant nor postpartum, adjusting for site and age produced no effect on the association between HIV and mortality (Table 6.7). HIV-infected women remained at approximately 20 times the risk of dying compared with uninfected women after adjusting for site and age (RR=19.8, 95% CI: 18.1-21.6).

Table 6.7: Mortality rates ratios from a Poisson regression model for non-pregnant nor postpartum women

	Number of deaths	Person-years	Mortality per 1,000 person-years (95% CI)	Crude mortality rate ratio (95% CI)	Adjusted mortality rate ratio (95% CI)
HIV status					
HIV-uninfected	652	231,804	2.8 (2.6-3.0)	1	1
HIV-infected	2939	50,859	57.8 (55.7-59.9)	20.5 (18.9-22.4)	19.8 (18.1-21.6)
Age group					
15-29	1,307	141,500	9.2 (8.7-9.8)	1	1
30-39	1,441	6,9475	20.7 (19.7-21.8)	2.2 (2.1-2.4)	1.3 (1.2-1.4)
40-49	843	71,689	11.8 (11.0-12.6)	1.3 (1.2-1.4)	1.1 (1.0-1.2)
Site name					
Karonga	135	19,794	6.8 (5.8-8.1)	1	1
Kisesa	286	46,592	6.1 (5.5-6.9)	0.9 (0.7-1.1)	1.1 (0.9-1.3)
Manicaland	787	28,023	28.1 (26.2-30.1)	4.1 (3.4-4.9)	2.1 (1.8-2.5)
Masaka	415	47,222	8.8 (8.0-9.7)	1.3 (1.1-1.6)	1.5 (1.2-1.8)
Rakai	907	83,666	10.8 (10.2-11.6)	1.6 (1.3-1.9)	1.1 (0.9-1.4)
uMkhanyakude	1,061	57,367	18.5 (17.4-19.6)	2.7 (2.3-3.2)	1.1 (0.9-1.3)

Abbreviations: CI=confidence interval

6.4 CONCLUSION

The data from the ALPHA network supports the conclusion from the systematic review that HIV-infected pregnant and postpartum women are at approximately eight times the risk of dying compared with their HIV-uninfected counterparts, and predict that around 24% of pregnancy-related deaths in sub-Saharan Arica are attributable to HIV. Sensitivity analyses suggest that these results are robust to assumptions that were made when assigning HIV and pregnancy status.

7 IDENTIFIYING HIV/AIDS-RELATED DEATHS USING VERBAL AUTOPSY DATA: EVIDENCE FROM THE NETWOK FOR ANALYSING LONGITUDINAL POPULATION-BASED HIV/AIDS DATA ON AFRICA (ALPHA)

7.1 INTRODUCTION

Through the work presented in this thesis so far, we have established that HIV-infected pregnant and postpartum women are at approximately eight times the risk of dying compared with their HIV-uninfected counterparts, and predicted that around a quarter of pregnancy-related deaths in sub-Saharan Arica are attributable to HIV.(98, 171) These HIV-attributable deaths are likely to be caused by both HIV/AIDS-related conditions (e.g. pneumocystis pneumonia and Kaposi's sarcoma) and other conditions through which HIV increases the risk of dying, but are not considered HIV/AIDS-related; however, the relative contribution of each of these is not well understood.

In a recent systematic review by Grollman and Ronsmans,(27) it was estimated that only 3% of all pregnancy-related deaths in sub-Saharan Africa are directly attributable to HIV/AIDS-related conditions based on 19 population-based studies using cause of death data. However, the authors concluded that the general quality of studies was poor, with few reporting criteria for assigning deaths to HIV/AIDS-related conditions. Higher percentages of deaths have been attributed to HIV/AIDS amongst only HIV-infected pregnant and postpartum women; in the 2008-2010 South African Confidential Enquiries into Maternal Deaths, 66% of HIV-infected maternal deaths had a CD4 count <200,(164) while in a facility-based, autopsy study conducted in Mozambique 28% of HIV-infected maternal deaths were attributed to HIV/AIDS-related conditions.(229)

Estimating the percentage of pregnancy-related deaths attributable to HIV/AIDS-related conditions has proved particularly challenging in regions with high HIV prevalence as often the HIV status of deaths is unknown and there is no systematic mortality surveillance. In the absence of vital registration systems and in areas where many deaths occur without medical supervision, cause of death can usually only be assessed through a verbal autopsy (VA).(24)

Physician review is the most commonly used method to interpret data from VAs.(23) This requires physicians to make a judgement on what they think is the most likely cause of death, given the reported signs and symptoms. Due to the subjective nature of physician review, each questionnaire is usually examined independently by two physicians, with a third reviewer consulted if there is disagreement. Besides being time consuming and expensive, physician review has been criticised for providing estimates which cannot be compared over different time periods and settings due to inconsistencies between physician reviewers.(23) Therefore, automated methods are being increasingly used to identify HIV/AIDS-related deaths from VAs, examples of which include a data-derived algorithm developed by Lopman *et al.*(94, 230) and a probabilistic model known as InterVA-4.(231)

The Lopman algorithm is a set of signs and symptoms extracted directly from VA data which are associated with optimum sensitivity and specificity in identifying "HIV/AIDS-related" deaths. HIV/AIDS-related deaths are defined as HIV-infected deaths not due to injury or direct obstetric causes.(94, 230) Direct obstetric deaths are defined as either deaths which occurred shortly before delivery, with excessive bleeding and/or severe headaches, or deaths during delivery.(230) The algorithm was initially developed and tested using a training data set which included a 75% sample of data from Manicaland, Zimbabwe,(230) identifying eight symptoms: weight loss, wasting, jaundice, herpes zoster, abscesses/sores, oral candidiasis, acute respiratory tract infection and vaginal tumors. This algorithm had a specificity of 78% and a sensitivity of 71% in the training data set, and a specificity of 76% and sensitivity of 66% amongst the remaining 25% of deaths. The algorithm was subsequently re-derived using data from both Manicaland and Kisesa, Tanzania, leading to the addition of one symptom, acute diarrhea.(94) To our knowledge, this algorithm has not been used to identify HIV/AIDS deaths amongst pregnant and postpartum women.

InterVA-4 is an expert-opinion algorithm (232, 233) which uses conditional probability, as outlined in Bayes' theorem, to calculate the probability of each cause of death from the reported signs and symptom using two sets of prior estimates which were defined by a panel of physicians:

1. The conditional probability of how likely a sign/symptom is, given a particular cause of death
2. An initial guess of the proportion of all deaths in a population due to each cause

InterVA-4 has been widely used to estimate causes of death, including HIV/AIDS-deaths.(90, 234, 235) A recent paper reported that InterVA-4 correctly identified 90.1% of HIV-uninfected deaths as not due to HIV/AIDS-related causes amongst all deaths in six of the ALPHA network sites.(26) Only one study included in the review on the percentage of pregnancy-related deaths attributed as HIV/AIDS-related by Grollman and Ronsmans(27) used InterVA-4 exclusively to determine the cause of death.(236) In this study, conducted in West Africa, 5.3% of deaths were classified as HIV/AIDS-related.

Understanding the causes of the excess pregnancy-related mortality attributable to HIV is key for directing interventions to prevent such deaths; however the extent to which estimates produced from VA data reflect the true cause-specific mortality fractions (CSMF) very much depends on the validity of the interpretation method. Therefore, the aim of this chapter is to assess the validity of the Lopman algorithm and InterVA-4 in identifying HIV/AIDS-related deaths amongst women of reproductive age, and to assess whether the validity of these methods varies by site or pregnancy status using VA data from three of the ALPHA network sites.

7.2 METHODS

7.2.1 Data sources

Data from three out of the six ALPHA sites which were included in the previous chapter could be used for this analysis: Karonga in Malawi, Kisesa in Tanzania and uMkhanyakude in South Africa.

Data from the remaining three sites were excluded as less than 45% of deaths received a verbal autopsy (VA). Furthermore, several key symptoms pertaining to HIV/AIDS-defining illnesses were not available for the sites in Uganda (e.g. oral candidiasis and swollen genitals in Masaka, and weight loss and herpes zoster in Rakai), while Manicaland in Zimbabwe had implausibly high reports for some key symptoms (e.g. over 90% of deaths had a positive response for rigidity).

Methods of VA data collection have already been described in Section 2.2.2.

7.2.2 Data preparation

Data analysts at each study site prepared data in a standard format. Each site extracted information including dates of study entry and dates of exit from the study, due to death or out-migration, and information on the HIV status of each study participant. Data were also extracted on the signs and symptoms reported in a VA; however the physician assignment of cause of death was not provided to ALPHA due to between-site differences in the methods of physician review (e.g. in the number of physicians which review the VAs and in the cause of death categories used).

Once the data were received we undertook a rigorous investigation of how the data for Karonga and Kisesa were transformed from the VA questionnaire to the standardised data format. For this, VA questionnaires for each site were examined and questions corresponding to a variable in the VA data specification were noted. This enabled us to look at variation in the questions used to create the variables both between the sites, and within sites over time (where the questionnaire changed). The results for some key symptoms are shown in Supplementary Table 1 (Appendix D).

We pooled data from all sites in July 2014. The VA data were then merged with the demographic surveillance site (DSS) data, and a VA was only retained for analysis if it

could be linked to a death which was recorded in the DSS. The VA data were then linked with data on HIV status from the serosurvey and on pregnancy status based on the DSS data. The methods for deriving HIV and pregnancy status have been described in detail in Section 2.2.4.

7.2.3 Data analysis

There are three main parts to the data analysis undertaken by the candidate, which can broadly be described as follows:

i. Description of VA data
ii. Validity of InterVA-4 and the Lopman algorithm for assigning HIV/AIDS-related deaths amongst women of reproductive age
iii. Validity of InterVA-4 and the Lopman algorithm for assigning cause of death by pregnancy status

These will each be explained in detail below.

7.2.3.1 Analysis section 1: Description of verbal autopsy data

First, we calculated VA coverage amongst women of reproductive age (i.e. how many deaths identified in the DSS had a VA) and looked at whether this varied by ART availability, age, whether they had ever been tested for HIV, and study site. A binomial log–linear regression model (237) was used to calculate the crude risk ratios (RiRs) for deaths having a VA by each of these variables. RiRs were calculated rather than odds ratios as the outcome was very common. All subsequent analyses were only conducted on the set of deaths which had a VA.

Between-site differences in the characteristics of the VA data were explored using a chi-squared test to assess whether there was statistical evidence for an association between study site and the distribution of deaths by ART availability. The time between death and the VA interview was also calculated, and summarised for each site using a box plot.

Finally, we explored the percentage of women missing data for the signs and symptoms reported in the VA. We looked at the percentage missing data for all signs and symptoms by site, and also examined the distribution of missing data by HIV status in the pooled data set for a subset of symptoms related to HIV/AIDS-defining illnesses.

For all further analyses, missing data were treated as a symptom being reported not to have occurred (the default InterVA-4 assumption).

These analyses were all performed using STATA version 13.

7.2.3.2 Analysis section 2: Assigning cause of death amongst women of reproductive age

All deaths with a VA were categorised by HIV status, and the distribution of deaths by HIV status overall, and by study site, was examined.

Estimating the percentage of deaths attributable to HIV/AIDS: Lopman Analysis

For the Lopman analysis, deaths were attributed to four broad cause of death groupings based on data extracted directly from the VA: injury-related, peripartum, HIV/AIDS-related and other causes of death. Overlap between these categories was explored, but ultimately each death was only assigned to a single cause in line with Lopman and colleagues.(94, 230) A death was categorised as injury-related if any of the "injury-related" symptoms listed in Table 7.1 had a positive response, and as peripartum if the death was not categorised as injury-related but had a positive response to one of the "peripartum" symptoms.

Table 7.1: Verbal autopsy symptoms used to categorise deaths as injury-related and peripartum

Injury-related	Peripartum
Any obvious recent injury?	Did she die in labour undelivered?
Was s/he in a transport accident?	Death within 24 hours of pregnancy ending
Did s/he drown?	
Had s/he fallen recently?	
Was s/he burnt by heat, steam or fire?	
Any poisoning, bite, sting?	
Was s/he intentionally injured by another person or people	
Was s/he injured by a force of nature	
Injured in some kind of violence or assault by another person	
Any suggestion of homicide?	
Any suggestion of suicide?	

A death was assigned to be HIV/AIDS-related if they had at least one symptom indicative of HIV/AIDS-related illnesses reported, and had not already been classified as either injury-related or peripartum. The set of symptoms indicative of HIV/AIDS-related illnesses were chosen to correspond closely to the set of symptoms derived by

Lopman and colleagues which are as follows: weight loss, vaginal tumours, wasting, herpes zoster, abscesses/sores, acute respiratory tract infection, jaundice, oral candidiasis, and diarrhoea. The definition of the symptoms used by Lopman *et al.* and the method of constructing these using the ALPHA data is presented in Table 7.2 (on p185). All deaths not assigned as injury-related, peripartum or HIV/AIDS-related were classified as "other".

The percentage of deaths to women of reproductive age assigned to each cause was calculated for each study site, overall and by HIV status. A sensitivity analysis was undertaken to explore the effect of not separating out the peripartum deaths.

The validity of the Lopman algorithm was then explored by looking at the specificity (i.e. the percentage of deaths to HIV-uninfected individuals correctly classified as not HIV/AIDS-related), for the Lopman symptoms individually and combined. It is possible that some of the "HIV-uninfected" deaths classified as HIV/AIDS-related, were in fact deaths to women who had seroconverted since their last HIV test. Therefore, time since last negative HIV test result was explored for those HIV-uninfected individuals assigned as dying from HIV/AIDS. Sensitivity (i.e. the percentage of HIV/AIDS-related deaths correctly identified as HIV/AIDS-related) could not be calculated based solely on the serosurvey data as it is to be expected that some HIV-infected individuals will die of causes other than HIV/AIDS. However, we report the percentage of HIV-infected deaths attributed to HIV/AIDS-related causes.

Table 7.2: Creating the signs and symptoms which were identified for the Lopman algorithm using the ALPHA data

Sign	Original definition in Lopman paper	Definition based on ALPHA data	Issues with the ALPHA approximation to Lopman definition
Weight loss	Moderate or severe weight loss with no other symptoms of malnutrition	Positive response to either: any weight loss OR any severe wasting AND no positive response to: any abnormal hair colouring OR any swelling of legs/ankles OR any anaemia/paleness	Not possible to distinguish those who had mild weight loss from those with moderate weight loss. No input to capture if someone has burning sensation of the feet or dry scaly skin ➢ Overestimate those with weight loss using ALPHA data?
Wasting	Moderate or severe weight loss with at least **4** of the following symptoms: paleness, changing hair colour, oedema of legs, burning sensation of the feet, dry scaly skin	Positive response to: any weight loss OR any severe wasting AND positive response to at least **2** of the following: any abnormal hair colouring AND/OR any swelling of legs/ankles AND/OR any anaemia/paleness	Not possible to distinguish those who had mild weight loss from those with moderate weight loss. No input to capture if someone has burning sensation of the feet or dry, scaly skin, so it was not possible to use 4 criteria ➢ Overestimate those with wasting using ALPHA data?
Jaundice	Acute jaundice (yellowing of the whites of the eyes during the disease that led to death) with fever and/or itching but without history of alcohol abuse	Positive response to: any yellowness/jaundice AND any fever AND Negative response to: was s/he known to drink alcohol	No data to capture itching. Alcohol variable probably includes those who drink moderately, not just those who have a history of alcohol abuse ➢ Underestimate those with Jaundice using ALPHA data?
Herpes Zoster	Ever suffered from zoster	Positive response to: any herpes zoster	None
Oral Candidiasis	Had at least two of the following: ulcers in the mouth, difficulty swallowing, white patches inside the mouth and tongue	Positive response to: any oral candidiasis	The ALPHA variable is likely to overestimate the % of oral candidiasis compared to the Lopman definition as for many of the sites this was based solely on whether there were white patches inside the mouth and tongue
Abscesses or sores	Had abscesses or sores	Positive response to: any ulcers/ abscesses or sores on the feet OR any ulcers/ abscesses or sores on body, apart from feet	None
Acute respiratory tract infection (ARTI)	Trouble breathing, cough lasting 3-26 days with fever but not recent TB, weight loss or wasting	Positive response to all of the following: any difficulty breathing AND duration of fever AND duration of cough (use report of any cough) Then removed if positive response to either: Lopman symptom wasting or weight loss OR any medical diagnosis of TB	Cough duration only given in categories classified as <2 weeks or ≥t2 weeks. Therefore could not exclude those with a cough lasting less than 3 days or greater than 26 days. ➢ Overestimate those with ARTI using ALPHA data?

Sign	Original definition in Lopman paper	Definition based on ALPHA data	Issues with the ALPHA approximation to Lopman definition
Vaginal tumours	Vaginal tumour for at least one month with or without bleeding	Positive response to: any lump or lesion in groin or genitals	There is no input to capture vaginal tumours – we are likely to overestimate the prevalence of vaginal tumours through the ALPHA data
Acute diarrhoea	Loose stools lasting 3-27 days	Positive response to: duration of diarrhoea (use report of diarrhoea lasting either <2 weeks or for 2-4 weeks)	It was not possible to exclude those with a diarrhoea lasting less than 3 days. ➢ Overestimate those with acute diarrhoea using ALPHA data?

Estimating the percentage of deaths attributable to HIV/AIDS: InterVA-4

To obtain CSMFs from InterVA-4, I converted the ALPHA VA data to the required InterVA-4 input format which is outlined in the InterVA-4 user guide.(231) The data were then run through the InterVA-4 model using R Studio (version 1.4).(238) InterVA-4 requires estimates of the prevalence of HIV and malaria among deaths in the population; these were both set to be high (>1% of all deaths) for Karonga and Kisesa, while for uMkhanyakude HIV was set at high and malaria was set at low.

All further analyses were carried out in STATA version 13. The output for InterVA-4 provides, for each individual, both the likelihood for every cause of death and the top three most likely causes of death. For the purpose of this analysis, causes of death were classified into seven broad groups as follows: HIV/AIDS-related deaths, pulmonary tuberculosis (TB), other infectious disease, non-communicable diseases, external causes and direct obstetric causes. Further details of the causes of death which contributed to each of these groups is given in Table 7.3.

Table 7.3: Grouping of InterVA-4 causes of death

Categories for analysis	InterVA-4 causes of death	
HIV/AIDS related	HIV/AIDS related	
Pulmonary tuberculosis	Pulmonary tuberculosis	
Other infectious diseases	Sepsis (non-obstetric)	
	Acute respiratory infection	
	Diarrhoeal diseases	
	Malaria	
	Measles	
	Meningitis and encephalitis	
	Tetanus	
	Pertussis	
	Haemorrhagic fever	
	Other and unspecified infect disease	
Non communicable diseases (NCD)	Oral neoplasms	Sickle cell with crisis
	Digestive neoplasms	Stroke
	Respiratory neoplasms	Other and unspecified cardiac dis
	Breast neoplasms	Chronic obstructive pulmonary dis
	Reproductive neoplasms	Asthma
	Other and unspecified neoplasms	Acute abdomen
	Severe anaemia	Liver cirrhosis
	Severe malnutrition	Renal failure
	Diabetes mellitus	Epilepsy
	Acute cardiac disease	Other and unspecified NCD

Categories for analysis	InterVA-4 causes of death	
External cause of death (CoD)	Road traffic accident	Assault
	Other transport accident	Other and unspecified external CoD
	Accidental fall	
	Accidental drowning and submersion	
	Accidental exposure to smoke, fire & flame	
	Contact with venomous plant/animal	
	Exposure to force of nature	
	Accidental poisoning and noxious subs	
	Intentional self-harm	
Direct obstetric causes	Ectopic pregnancy	
	Abortion-related death	
	Pregnancy-induced hypertension	
	Obstetric haemorrhage	
	Obstructed labour	
	Pregnancy-related sepsis	
	Anaemia of pregnancy	
	Ruptured uterus	
	Other and unspecified maternal CoD	

The CSMFs were calculated, by site and HIV status, by summing the likelihood of each cause of death across all individuals within a given subgroup. This is in line with the recommended method for using InterVA-4.(231) The effect of calculating the CSMF by using the most likely cause assigned to each death was also explored.

The percentage of deaths attributed to HIV/AIDS amongst the HIV-infected deaths was reported. The specificity of InterVA-4 was calculated by subtracting the percentage of deaths attributed to HIV/AIDS amongst the HIV-uninfected from 100. Time since the last negative test was investigated for those individuals classified as HIV-uninfected which were assigned HIV/AIDS as the most likely cause.

Estimating the percentage of deaths attributable to HIV/AIDS: Comparison of the Lopman algorithm and InterVA-4

Whilst it was not possible to calculate sensitivity, we compared the percentage of HIV-infected deaths assigned to be HIV/AIDS-related using the Lopman algorithm and InterVA-4 with the attributable risk percentage (AR%). The AR% provides a measure of the percentage of HIV-infected deaths attributable to HIV/AIDS by subtracting the all-cause mortality rate in HIV-uninfected women from that in HIV-infected women. This

was presented for the pooled data in Chapter 6, but for the purpose of this comparison was re-calculated by site for the pooled data sub-set used throughout this chapter.

We then explored how the percentage of deaths estimated to be HIV/AIDS-related would vary by the actual percentage of deaths that are HIV/AIDS-related given the specificities observed for the Lopman algorithm and InterVA-4. We replicated this analysis, first assuming sensitivity was 100% for both methods and then assuming a sensitivity of 80%.

7.2.3.3 Analysis section 3: Validity of methods for assigning cause of death by pregnancy status

In the final analysis section, we categorised the deaths by pregnancy status (pregnant and up to 42 days postpartum/not pregnant or up to 42 days postpartum), examined whether this information on pregnancy was ascertained from the VA and/or the DSS data, and calculated the percentage of deaths which were pregnancy-related at each site.

We explored whether the validity of the Lopman algorithm and InterVA-4 varied by pregnancy status by calculating the percentage of deaths assigned to each cause by pregnancy and HIV status, and calculating the specificity.

7.3 RESULTS

7.3.1 Description of verbal autopsy data

A total of 4,143 deaths to women of reproductive ages were identified from the three demographic surveillance sites (DSS). The majority of these deaths were from uMkhanyakude (N=3,133), with 632 deaths from Karonga and 378 from Kisesa.

Verbal autopsy coverage

Of the 4,143 deaths to women of reproductive age identified through the DSS, 3,642 (87.9%) had a verbal autopsy (VA). Table 7.4 shows the number of deaths reported in the DSS, and the percentage of these deaths which had a VA by several characteristics. Levels of VA coverage were lower amongst deaths which occurred since ART became widely available, amongst deaths to women aged 15-19 and for those who were ever tested for HIV (p<0.001). There was also strong evidence for differences between the sites with VA coverage ranging from 75.9% in Kisesa to 99.5% in Karonga (p<0.001).

Table 7.4: Verbal autopsy coverage and the association between study characteristics and risk of getting a verbal autopsy amongst women of reproductive age

		Number of DSS deaths	Number of deaths with a VA	% of DSS deaths with a VA	Crude risk ratio (95% CI)	p-value
ART availability	ART fully available	1685	1301	77.2	1	
	ART roll out	786	774	98.5	1.28 (1.24-1.31)	
	Pre-ART	1672	1567	93.7	1.21 (1.18-1.25)	<0.001
Age at death	15-19	218	182	83.5	1	
	20-29	1342	1199	89.3	1.07 (1.01-1.14)	
	30-39	1540	1347	87.5	1.05 (0.98-1.11)	
	40-49	1043	914	87.6	1.05 (0.99-1.12)	<0.001
Ever had an HIV test	Never tested	2157	1968	91.2	1	
	Ever tested	1986	1674	84.3	0.92 (0.90-0.95)	<0.001
Study	uMkhanyakude	3133	2786	88.9	1	
	Kisesa	632	480	75.9	0.88 (0.85-0.91)	
	Karonga	378	376	99.5	1.11 (1.09-1.13)	<0.001

Abbreviations: DSS = Demographic Surveillance Site, VA=Verbal Autopsy

Between-site differences in the verbal autopsy data

There are several notable differences between the sites. In Kisesa, 64.0% of deaths occurred before ART became available compared with 37.6% in uMkhanyakude and 48.4% in Karonga (p<0.001). The sites varied in the length of time between the date of

death and the VA interview date, with the shortest median time found in Karonga (33 days), and the highest found in Kisesa (278 days). This is illustrated in Figure 7.1.

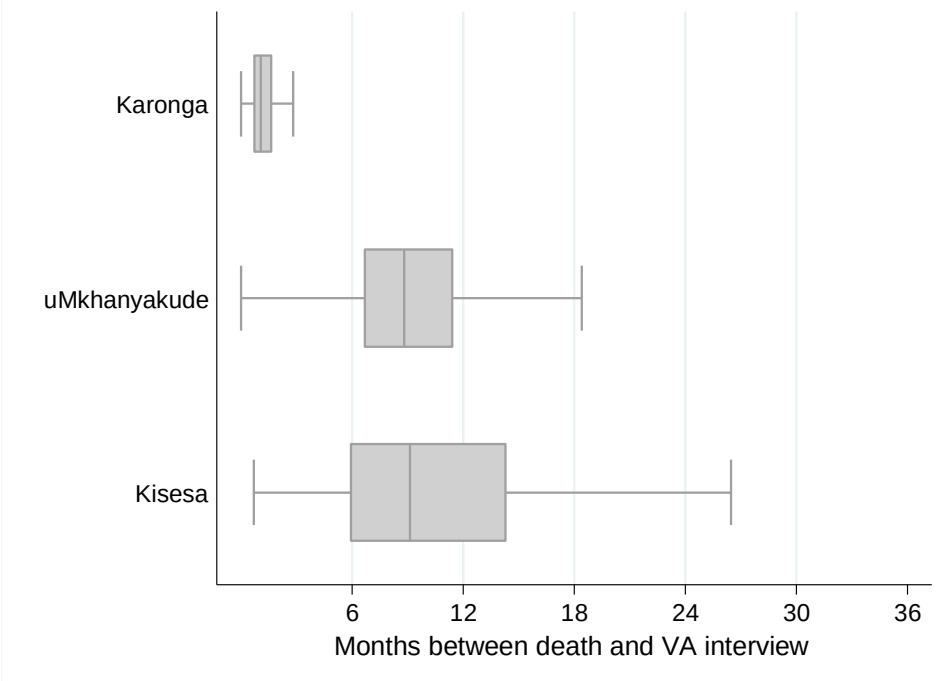

Figure 7.1: Box plot showing of the number of months between date of death and verbal autopsy (VA) interview for women of reproductive age (excludes outliers)

Missing data

Of the 3,642 deaths with a VA, 147 (4.0%) were dropped by InterVA-4 due to missing data. Further exploration of the deaths dropped by InterVA-4 showed that one death could have been classified as injury-related in the Lopman analysis, but the remaining 146 deaths would have been classified in the "other" cause of death category due to lack of useful information. These deaths were therefore excluded and the final sample size for all analyses was 3,495.

Table 7.5 shows the percentage of deaths missing the key HIV/AIDS symptoms by site. In Karonga, six symptoms were missing for more than 50% of the deaths, compared with three in both Kisesa and uMkhanyakude. The symptoms missing substantial amounts of data varied between the sites. For example, "any medical diagnosis of tuberculosis" had missing data for 0.3% of deaths in uMkhanyakude, compared with 3.5% in Karonga and 51.9% in Kisesa. Similarly, the percentage of deaths with missing data for "any herpes zoster" was 10.4%, 17.9% and 85.8% in uMkhanyakude, Kisesa and Karonga, respectively.

Table 7.5: Number of deaths with missing data for the key HIV/AIDS symptoms, by site

Symptoms for identifying HIV/AIDS deaths	Karonga (N=374) N (%)	Kisesa (N=441) N (%)	uMkhanyakude (N=2680) N (%)	All sites (N=3,495) N (%)
Any medical diagnosis of HIV/AIDS	163 (43.6)	73 (16.6)	8 (0.3)	244 (7.0)
Any weight loss	5 (1.3)	21 (4.8)	78 (2.9)	104 (3.0)
Any severe wasting	179 (47.9)	72 (16.3)	99 (3.7)	350 (10.0)
Any abnormal hair colouring	335 (89.6)	240 (54.4)	2256 (84.2)	2831 (81.0)
Any swelling of legs/ankles	14 (3.7)	30 (6.8)	412 (15.4)	456 (13.0)
Any anaemia/paleness	16 (4.3)	15 (3.4)	463 (17.3)	494 (14.1)
Any yellowness/jaundice	5 (1.3)	16 (3.6)	645 (24.1)	666 (19.1)
How long did fever last	15 (4.0)	0 (0)	1 (0)	16 (0.5)
Any herpes zoster	321 (85.8)	79 (17.9)	280 (10.4)	680 (19.5)
Any oral candidiasis	281 (75.1)	65 (14.7)	3 (0.1)	349 (10.0)
Any ulcers/ abscesses or sores on the feet	374 (100)	277 (62.8)	2409 (89.9)	3060 (87.6)
any ulcers/ abscesses or sores on body, apart from feet	374 (100)	26 (5.9)	2409 (89.9)	2809 (80.4)
Any difficulty breathing	374 (100)	216 (49.0)	1 (0.0)	591 (16.9)
How long did cough last	7 (1.9)	12 (2.7)	91 (3.4)	110 (3.1)
Any medical diagnosis of tuberculosis	13 (3.5)	229 (51.9)	7 (0.3)	249 (7.1)
Any lump or lesion in groin or genitals	19 (5.1)	27 (6.1)	527 (19.7)	573 (16.4)
How long did diarrhoea last	4 (1.1)	10 (2.3)	4 (0.1)	18 (0.5)

In uMkhanyakude, no deaths could be classified as peripartum as there were missing data for both the key symptoms (Table 7.6). In Karonga, there was no information on whether a woman died in labour undelivered, but complete information on whether the death occurred within 24 hours of pregnancy ending. Kisesa had high levels of missing data for both symptoms (≥80%). Missing data for symptoms used to identify injury deaths are also shown in Table 7.6, while the missing data for all other symptoms are given in Supplementary Table 2 (Appendix D).

Table 7.6: Percentage of deaths with missing data for symptoms for identifying obstetric and injury deaths, by site

	Karonga (N=374) N (%)	Kisesa (N=441) N (%)	uMkhanyakude (N=2680) N (%)	All sites (N=3,495) N (%)
Peripartum deaths[1]				
Did she die in labour undelivered	47 (100)	47 (79.7)	71 (100)	165 (93.2)
Death within 24 hours of pregnancy ending	0 (0)	50 (84.7)	71 (100)	121 (68.4)
Injury deaths				
Any obvious recent injury	369 (98.7)	26 (5.9)	3 (0.1)	398 (11.4)
Was s/he in a transport accident	5 (1.3)	220 (49.9)	600 (22.4)	825 (23.6)
Did s/he drown	12 (3.2)	220 (49.9)	600 (22.4)	832 (23.8)
Had s/he fallen recently	5 (1.3)	220 (49.9)	600 (22.4)	825 (23.6)
Was s/he burnt by heat steam or fire	5 (1.3)	228 (51.7)	611 (22.8)	844 (24.1)
Any poisoning, bite, sting	5 (1.3)	220 (49.9)	2680 (100)	2905 (83.1)
Was s/he intentionally injured by another person or people	374 (100)	194 (44.0)	610 (22.8)	1178 (33.7)
Was s/he injured by a force of nature	374 (100)	441 (100)	2680 (100)	3495 (100)
Injured in some kind of violence or assault by another person	5 (1.3)	228 (51.7)	599 (22.4)	832 (23.8)
Any suggestion of homicide	368 (98.4)	139 (31.5)	610 (22.8)	1117 (32.0)
Any suggestion of suicide	8 (2.1)	144 (32.7)	599 (22.4)	751 (21.5)

[1]**Denominator is the number of pregnancy-related deaths: 47 in Karonga, 59 in Kisesa and 71 in uMkhanyakude**

Table 7.7 shows the percentage of deaths with missing data for the key HIV/AIDS symptoms, stratified by HIV status. Compared with uninfected deaths, a higher percentage of HIV-infected individuals were missing data on abnormal hair colouring, swelling of legs, yellowness/jaundice, ulcers/abscesses and vaginal lumps. The reverse was true for the following symptoms: medical diagnosis of HIV/AIDS, weight loss, wasting, herpes zoster, oral candidiasis, difficulty breathing, cough and medical diagnosis of TB.

Table 7.7: Percentage of deaths with missing data for key HIV/AIDS symptoms in the pooled data, by HIV status

Symptoms for identifying HIV/AIDS deaths	HIV negative (N=233) N (%)	HIV positive (N=1380) N (%)	HIV status unknown (N=1882) N (%)	All women (N=3495) N (%)
Any medical diagnosis of HIV/AIDS	30 (12.9)	74 (5.4)	140 (7.4)	244 (7.0)
Any weight loss	7 (3.0)	7 (0.5)	90 (4.8)	104 (3.0)
Any severe wasting	26 (11.2)	128 (9.3)	196 (10.4)	350 (10.0)
Any abnormal hair colouring	147 (63.1)	1165 (84.4)	1519 (80.7)	2831 (81.0)
Any swelling of legs/ankles	10 (4.3)	103 (7.5)	343 (18.2)	456 (13.0)
Any anaemia/paleness	15 (6.4)	85 (6.2)	394 (20.9)	494 (14.1)
Any yellowness/jaundice	11 (4.7)	133 (9.6)	522 (27.7)	666 (19.1)
How long did fever last	1 (0.4)	8 (0.6)	7 (0.4)	16 (0.5)
Any herpes zoster	60 (25.8)	212 (15.4)	408 (21.7)	680 (19.5)
Any oral candidiasis	50 (21.5)	133 (9.6)	166 (8.8)	349 (10.0)
Any ulcers/ abscesses or sores on the feet	186 (79.8)	1203 (87.2)	1671 (88.8)	3060 (87.6)
any ulcers/ abscesses or sores on body, apart from feet	121 (51.9)	1128 (81.7)	1560 (82.9)	2809 (80.4)
Any difficulty breathing	120 (51.5)	240 (17.4)	231 (12.3)	591 (16.9)
How long did cough last	5 (2.1)	17 (1.2)	88 (4.7)	110 (3.1)
Any medical diagnosis of tuberculosis	63 (27.0)	80 (5.8)	106 (5.6)	249 (7.1)
Any lump or lesion in groin or genitals	9 (3.9)	99 (7.2)	465 (24.7)	573 (16.4)
How long did diarrhoea last	1 (0.4)	7 (0.5)	10 (0.5)	18 (0.5)

7.3.2 Cause of death amongst women of reproductive age

Distribution of deaths by HIV status

Overall, 46.2% of the deaths to women of reproductive age had known HIV status; however, this varied from 41.9% in uMkhanyakude to 62.3% in Karonga (Table 7.8). Amongst the deaths with known HIV status, more were HIV-infected than uninfected. In uMkhanyakude, 95.2% of deaths with known HIV status were HIV-infected, compared with 72.5% and 55.1% in Karonga and Kisesa, respectively. Therefore, in the final pooled sample most of the HIV-infected deaths come from uMkhanyakude (the site with the highest overall HIV prevalence) while most of the HIV-uninfected deaths come from Kisesa.

Table 7.8: Distribution of deaths with a verbal autopsy by study and HIV status

	Number of deaths	Number of deaths which are HIV+ (%)	Number of deaths which of deaths which are HIV- (%)	Number of deaths with unknown HIV status (%)
Karonga	374	169 (45.2)	64 (17.1)	141 (37.7)
Kisesa	441	141 (32.0)	115 (26.1)	185 (42.0)
uMkhanyakude	2680	1070 (39.9)	54 (2.0)	1556 (58.1)
All Sites	3495	1380 (39.5)	233 (6.7)	1882 (53.8)

Lopman algorithm: cause of death distribution

Overall, 147 (4.2%) of deaths were classified as injuries/accidents, 15 (0.4%) as peripartum and 2,618 (74.9%) as HIV/AIDS-related (Table 7.9). Of the 147 deaths classified as due to injuries/accidents, none had symptoms of “peripartum deaths” reported while 25 had “HIV/AIDS-related” symptoms present. Only one of the 15 deaths classified as peripartum had “HIV/AIDS-related” symptoms reported.

Regional variations in the cause of death distributions were evident with 52.1% of deaths attributed to HIV/AIDS in Karonga, 61.2% in Kisesa and 80.3% in uMkhanyakude. No deaths could be attributed as peripartum in uMkhanyakude as information was not collected on these symptoms in the VA. Reclassifying the peripartum deaths from the other two sites did not alter the results substantially (Appendix D, Supplementary Table 3).

Table 7.9: Cause of death ascertained using the Lopman algorithm, by site

	Number of deaths	Number of deaths assigned to:			
		Injuries/ Accidents (%)	Peripartum (%)	HIV/AIDS (%)	Other (%)
Karonga	374	10 (2.7)	10 (2.7)	195 (52.1)	159 (42.5)
Kisesa	441	29 (6.6)	5 (1.1)	270 (61.2)	137 (31.1)
uMkhanyakude	2680	108 (4.0)	-	2153 (80.3)	419 (15.6)
All sites	3495	147 (4.2)	15 (0.4)	2618 (74.9)	715 (20.5)

Lopman algorithm: validity in assigning HIV/AIDS deaths

Table 7.10 shows the cause of death distributions stratified by HIV status. Overall, 36.1% of HIV-uninfected deaths are classified as HIV/AIDS-related, hence the Lopman algorithm correctly classified 63.9% of HIV-uninfected deaths as non-HIV/AIDS-related. The specificity of the Lopman algorithm varied by site, ranging from 59.1% in Kisesa to 75.0% in Karonga. The percentage of HIV-infected deaths which were classified as HIV/AIDS-related was 63.9% in Karonga, 85.1% in Kisesa and 87.8% in uMkhanyakude.

Table 7.10: Cause of death distributions assigned using the Lopman algorithm, stratified by HIV status and site

	Number of deaths	Number of deaths assigned to:			
		Injuries/ Accidents (%)	Peripartum (%)	HIV/AIDS (%)	Other (%)
Karonga					
HIV negative	64	5 (7.8)	5 (7.8)	16 (25.0)	38 (59.4)
HIV positive	169	1 (0.6)	1 (0.6)	108 (63.9)	59 (34.9)
HIV status unknown	141	4 (2.8)	4 (2.8)	71 (50.4)	62 (44.0)
Kisesa					
HIV negative	115	14 (12.2)	3 (2.6)	47 (40.9)	51 (44.3)
HIV positive	141	2 (1.4)	0 (0)	120 (85.1)	19 (13.5)
HIV status unknown	185	13 (7.0)	2 (1.1)	103 (55.7)	67 (36.2)
uMkhanyakude					
HIV negative	54	12 (22.2)	0 (0)	21 (38.9)	21 (38.9)
HIV positive	1070	20 (1.9)	0 (0)	939 (87.8)	111 (10.4)
HIV status unknown	1556	76 (4.9)	0 (0)	1193 (76.7)	287 (18.4)
All sites					
HIV negative	233	31 (13.3)	8 (3.4)	84 (36.1)	110 (47.2)
HIV positive	1380	23 (1.7)	1 (0.1)	1167 (84.6)	189 (13.7)
HIV status unknown	1882	93 (4.9)	6 (0.3)	1367 (72.6)	416 (22.1)

As shown in Table 7.11, the symptoms with the lowest specificity were diarrhoea and weight loss in the pooled data set. In Karonga weight loss had the lowest specificity, whereas diarrhoea had the lowest specificity in the other two sites.

Table 7.11: Specificity of the Lopman algorithm, and the individual signs and symptoms which make up the algorithm, for the ALPHA data set, overall and by site

	Overall (No. of HIV- deaths=233)		Karonga (No. of HIV- deaths=64)		Kisesa (No. of HIV- deaths=115)		uMkhanyakude (No. of HIV- deaths=54)	
	Number without symptom(s)	Specificity	Number without symptom(s)	Specificity	Number without symptom(s)	Specificity	Number without symptom(s)	Specificity
Lopman algorithm (any one of the 9 symptoms)	149	63.9	48	75.0	68	59.1	33	61.1
Weight loss	207	88.8	52	81.3	108	93.9	47	87.0
Vaginal tumours	226	97.0	64	100	108	93.9	54	100
Wasting	222	95.3	64	100	104	90.4	54	100
Herpes Zoster	232	99.6	64	100	114	99.1	54	100
Abscesses / sores	220	94.4	64	100	105	91.3	51	94.4
ARTI	228	97.9	64	100	114	99.1	50	92.6
Jaundice	215	92.3	61	95.3	100	87.0	54	100
Oral Candidiasis	214	91.8	63	98.4	108	93.9	43	79.6
Diarrhoea	193	82.8	60	93.8	92	80.0	41	75.9

The median time between the last negative test and death for the 84 deaths which were classified as HIV negative based on serostatus but identified as HIV/AIDS-related based on the Lopman symptoms was nine months (Inter-quartile range: 4.3-20.4 months) but with regional variation (Figure 7.2).

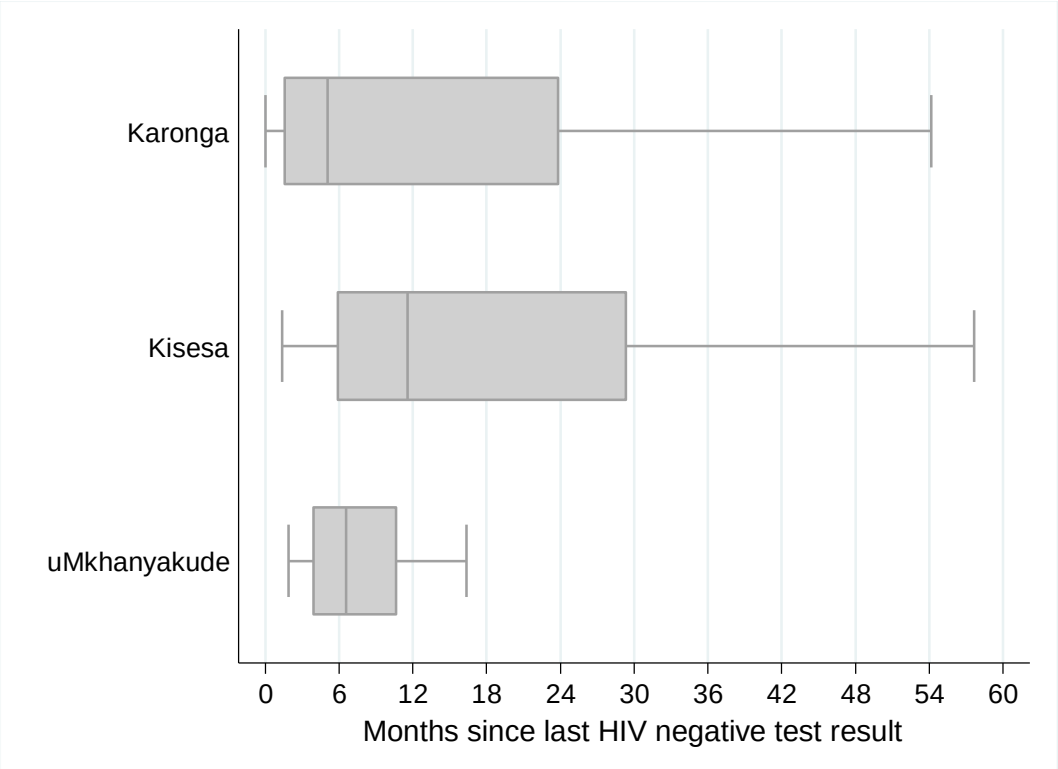

Figure 7.2: Box plot showing the time from last negative HIV test result to deaths for HIV-negative people assigned HIV/AIDS-related as the cause of death based on the Lopman symptoms

InterVA-4: cause of death distribution

The CSMFs by site are shown in Table 7.12. Overall, 33.8% of deaths to women of reproductive age were attributed to HIV/AIDS by InterVA-4. 32.2% of deaths in uMkhanyakude were assigned as HIV/AIDS-related compared with 42.1% in Kisesa and 35.2% in Karonga. A very high percentage of all deaths were classified as TB (38.4%), but this appeared to be driven largely by uMkhanyakude where nearly half of deaths were assigned as TB. In Karonga, other infectious diseases accounted for a high percentage of deaths at 24.3%, while in Kisesa 25.3% of deaths were classified as non-communicable.

Using the most likely cause of death did not lead to substantial changes in the CSMF, compared with summing the likelihood of each cause of death across all deaths (Appendix D, Supplementary Table 4).

Table 7.12: Cause of death ascertained using InterVA-4, by site

	Number of deaths	Percentage of deaths assigned to:					
		HIV/ AIDS	TB	Other infectious diseases	NCD	External causes	Direct obstetric causes
Karonga	3495	35.2	14.6	24.3	15.5	3.2	7.1
Kisesa	815	42.1	8.4	8.9	25.3	4.7	10.6
uMkhanyakude	2680	32.2	46.7	4.9	10.6	3.9	1.7
All sites	3495	33.8	38.4	7.5	13	3.9	3.4

InterVA-4: validity in assigning HIV/AIDS deaths

Amongst the HIV-uninfected deaths, 17.3% were attributed to HIV/AIDS (10.5% in Karonga, 21.1% in Kisesa and 17.4% in uMkhanyakude) (Table 7.13). Therefore, the specificity was 82.7%, ranging from 78.9% in Kisesa to 89.5% in Karonga. The percentage of deaths attributed to HIV/AIDS amongst the HIV-infected was particularly low in uMkhanyakude (37.4%), compared with Karonga (47.1%) and Kisesa (63.2%). However, across all sites a higher percentage of the HIV-infected deaths were assigned TB as a cause of death compared with uninfected deaths. Reclassifying the TB deaths as HIV/AIDS-related increased the estimates of HIV/AIDS-related deaths amongst the HIV-infected to 65.9% in Karonga, 72.7% in Kisesa and 86.3% in uMkhanyakude; however, this also led to a drop in specificity to 63.8% in uMkhanyakude, 72.6% in Kisesa and 77.9% in Karonga.

Table 7.13: Cause of death distributions assigned using InterVA-4, stratified by HIV status and site

	Number of deaths	Percentage of deaths assigned to:					
		HIV/ AIDS	TB	Other infectious diseases	NCD	External causes	Direct obstetric causes
Karonga							
HIV negative	64	10.5	11.6	32.1	15.8	8.9	21.1
HIV positive	169	47.1	18.8	20.9	11.2	0.3	1.8
HIV status unknown	141	32.3	10.9	24.9	20.6	4.2	7.2
Kisesa							
HIV negative	115	21.1	6.3	12.1	32.4	9.2	18.9
HIV positive	141	63.2	9.5	6.1	17.1	0	4
HIV status unknown	185	39.0	8.8	9.1	27	5.6	10.5
uMkhanyakude							
HIV negative	54	17.4	18.8	6.3	29.9	22	5.7
HIV positive	1070	37.4	48.9	3.8	7.4	1.8	0.7
HIV status unknown	1556	29.1	46.2	5.6	12.1	4.7	2.3
All sites							
HIV negative	233	17.3	10.6	16.3	27.2	12.1	16.4
HIV positive	1380	41.2	41.2	6.1	8.8	1.4	1.2
HIV status unknown	1882	30.3	39.9	7.4	14.2	4.7	3.4

Comparison of methods: implications for calculating the percentage of deaths attributable to HIV/AIDS

Comparison of the AR% (calculated by comparing mortality rates in HIV-infected women to those in uninfected women) and the percentage of HIV-infected deaths attributed to HIV/AIDS using the Lopman algorithm and InterVA-4 is presented in Table 7.14. Across all sites, the AR% provides a higher estimate of the percentage of deaths attributable to HIV/AIDS than the methods using the VA data.

Table 7.14: Percentage of deaths attributed to HIV/AIDS using different methods

	Number of HIV-infected deaths	Percentage of HIV-infected deaths attributed to HIV/AIDS based on:			
		Attributable Risk Percentage	Lopman Algorithm	InterVA-4 (HIV/AIDS)	InterVA-4 (HIV/AIDS/TB)
Karonga	169	95.7	63.9	47.1	65.9
Kisesa	141	92.0	85.1	63.2	72.7
uMkhanyakude	1070	94.3	87.8	37.4	86.3
All sites	1380	93.0	84.6	41.2	82.4

Overall, the specificity of the methods in identifying HIV/AIDS-related deaths was 69.3% for the Lopman algorithm, 82.7% for InterVA-4 when TB deaths were treated as

not HIV/AIDS-related, and 72.1% for InterVA-4 when TB deaths were included as HIV/AIDS-related.

Figure 7.3 shows how the percentage of deaths estimated to be HIV/AIDS-related varies by the actual percentage of deaths that are HIV/AIDS-related given the range of specificity observed for the Lopman algorithm and InterVA-4, and given a sensitivity of 100%. Assuming 100% sensitivity and a specificity of less than 100% will always lead to an overestimate in the percentage of deaths attributable to HIV/AIDS; however, the degree to which the percentage is overestimated for a given specificity decreases as the actual percentage of deaths attributable to HIV/AIDS increases. For example, based on the specificity observed for InterVA-4 including TB deaths (72.1%), 31.5% of deaths would be predicted to be attributable to HIV/AIDS when the actual percentage is 5%. When the actual percentage is 50%, 64.0% of deaths would be attributed to HIV/AIDS.

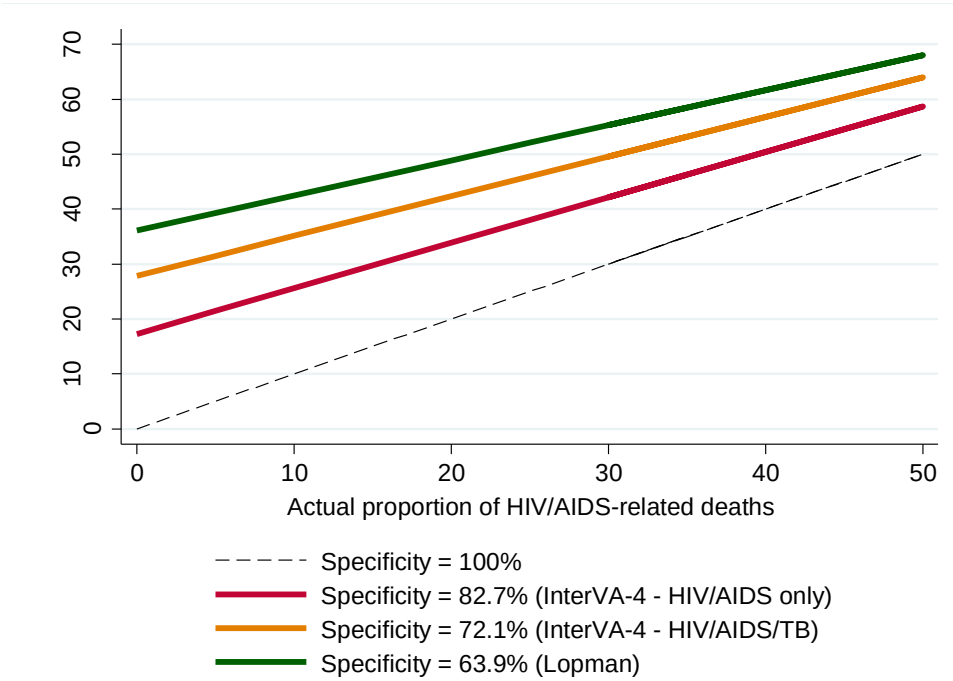

Figure 7.3: Estimated percentage of HIV/AIDS-related deaths over a range of specificities plotted against the actual percentage of HIV/AIDS-related deaths (assuming sensitivity of 100%)

With a sensitivity of 80%, we see a lower level of over-estimation of the percentage of deaths based on the specificity of the InterVA-4 using the HIV/AIDS/TB definition and for the Lopman algorithm when the actual prevalence of HIV/AIDS-related deaths is up to 50% (Figure 7.4). For the InterVA-4 specificity when we do not include TB as

HIV/AIDS-related deaths, there is a slight underestimate of the percentage of deaths attributable to HIV/AIDS when the actual percentage reaches 50%.

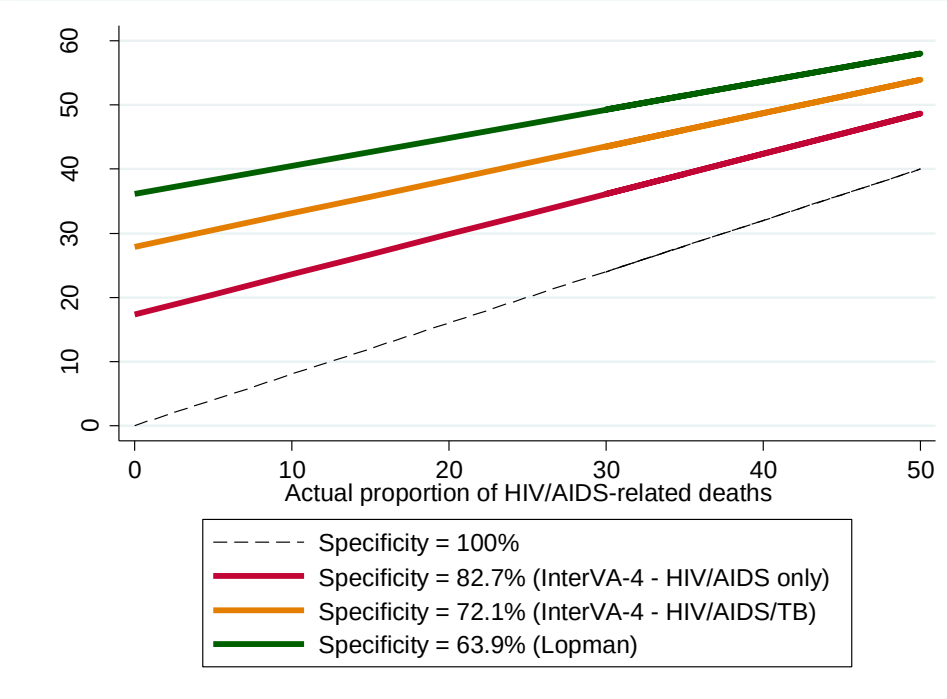

Figure 7.4: Estimated percentage of HIV/AIDS-related deaths over a range of specificities plotted against the actual percentage of HIV/AIDS-related deaths (assuming sensitivity of 80%)

7.3.3 Cause of death by pregnancy status

Deaths by HIV and pregnancy status

Of the 3,495 deaths, 177 were identified as being pregnant or up to 42 days postpartum. Most (n=148, 83.6%) of these deaths were identified as pregnancy-related using the VA data (Table 7.15). Two deaths in Kisesa were not reported to have been pregnant/postpartum in the VA, yet had circumstances indicative of a pregnancy (both had “professional assistance at delivery” and “delivery by caesarean-section” reported, and one also had a report of smelly vaginal discharge). These were therefore reclassified to be pregnancy-related.

Table 7.15: Number of pregnancy-related deaths by source of information and study site

	Karonga	Kisesa	uMkhanyakude	Total
Identified in DSS and VA	12	6	19	37
Identified in DSS only	4	1	22	27
Identified in VA only	31	50	30	111
Identified from VA pregnancy symptoms	0	2	0	2
Total from both sources allowing for overlap	47	59	71	177

Abbreviations: DSS = Demographic Surveillance Site, VA=Verbal Autopsy

The percentage of deaths which were pregnancy-related ranged from 2.6% in uMkhanyakude to 13.4% in Kisesa (Table 7.16). Of the pregnancy-related deaths, 53.7% had known HIV status compared with 45.8% of the other deaths. Across all sites, pregnancy-related deaths were less likely to be HIV-infected than non-pregnancy-related deaths. This was particularly pronounced in Karonga where 14.9% of pregnancy-related deaths were HIV-infected compared with 49.5% of the other deaths.

Table 7.16: Distribution of deaths with a verbal autopsy by study, pregnancy and HIV status

	Number of deaths	Number of deaths which are HIV+ (%)	Number of deaths which are HIV- (%)	Number of deaths with unknown HIV status (%)
Karonga				
Not pregnant or postpartum	327	162 (49.5)	42 (12.8)	123 (37.6)
Pregnant or postpartum	47	7 (14.9)	22 (46.8)	18 (38.3)
Kisesa				
Not pregnant or postpartum	382	132 (34.6)	87 (22.8)	163 (42.7)
Pregnant or postpartum	59	9 (15.3)	28 (47.5)	22 (37.3)
uMkhanyakude				
Not pregnant or postpartum	2609	1044 (40.0)	51 (2.0)	1514 (58.0)
Pregnant or postpartum	71	26 (36.6)	3 (4.2)	42 (59.2)
All Sites				
Not pregnant or postpartum	3318	1338 (40.3)	180 (5.4)	1800 (54.2)
Pregnant or postpartum	177	42 (23.7)	53 (29.9)	82 (46.3)

Lopman algorithm: validity by pregnancy status

There is marked variation in the percentage of deaths attributed to HIV/AIDS by pregnancy status, with 77.3% of deaths attributed to HIV/AIDS in non-pregnant or postpartum women, compared with 29.9% amongst pregnancy-related deaths (Table 7.17). Within both groups, HIV-infected women are most likely to be classified as HIV/AIDS-related deaths (85.5% amongst non-pregnant and postpartum deaths and 54.8% amongst pregnant and postpartum women). However, 41.1% of deaths to non-

pregnant or postpartum women and 18.9% of pregnancy-related deaths are classified as HIV/AIDS-related, despite having a recent HIV-negative test. The algorithm therefore had higher specificity in pregnant and postpartum women compared to their non-pregnant counterparts (81.1% versus 58.9%). The cause of death distributions by pregnancy status for each site are given in Supplementary Table 5 (Appendix D).

Table 7.17: Cause of death ascertained using the Lopman algorithm, by pregnancy and HIV status

	Number of deaths	Number of deaths assigned to:			
		Injuries/ Accidents (%)	Peripartum (%)	HIV/AIDS (%)	Other (%)
Pregnant or up to 42 days postpartum					
HIV negative	53	2 (3.8)	8 (15.1)	10 (18.9)	33 (62.3)
HIV positive	42	1 (2.4)	1 (2.4)	23 (54.8)	17 (40.5)
HIV status unknown	82	1 (1.2)	6 (7.3)	20 (24.4)	55 (67.1)
Overall	177	4 (2.3)	15 (8.5)	53 (29.9)	105 (59.3)
Not pregnant or up to 42 days postpartum					
HIV negative	180	29 (16.1)	0 (0)	74 (41.1)	77 (42.8)
HIV positive	1338	22 (1.6)	0 (0)	1144 (85.5)	172 (12.9)
HIV status unknown	1800	92 (5.1)	0 (0)	1347 (74.8)	361 (20.1)
Overall	3318	143 (4.3)	0 (0)	2565 (77.3)	610 (18.4)

InterVA-4: validity by pregnancy status

Only 19.2% of pregnancy-related deaths were classified as HIV/AIDS-related, compared with 34.5% of non-pregnancy-related deaths (Table 7.18). The percentage of HIV-uninfected deaths attributed to HIV/AIDS was 7.9% in pregnant and postpartum women and 20.1% amongst the other deaths. Therefore, InterVA-4 correctly classified 92.1% of pregnancy-related and 79.9% of non-pregnancy-related HIV-uninfected deaths as non-HIV/AIDS-related. In both pregnant and non-pregnant women, the percentage of deaths attributed to pulmonary TB was much higher in HIV-infected compared with HIV-uninfected women. Site-specific results are given in Supplementary Table 6 (Appendix D).

Table 7.18: Cause of death distributions assigned using InterVA-4 in the pooled data, stratified by HIV and pregnancy status

	Number of deaths	Percentage of deaths assigned to:					
		HIV/ AIDS	Pulmonary TB	Other infectious diseases	NCD	External causes	Direct obstetric causes
Pregnant or up to 42 days postpartum							
HIV negative	53	7.9	3.5	14.2	11.0	0.9	62.5
HIV positive	42	36.0	15.0	5.3	15.1	0	28.6
HIV status unknown	82	17.8	5.3	4.8	17.9	2.2	51.9
Overall	177	19.2	7.1	7.7	15.2	1.3	49.6
Not pregnant or up to 42 days postpartum							
HIV negative	180	20.1	12.7	16.9	32.0	15.4	2.9
HIV positive	1338	41.4	42.0	6.2	8.6	1.5	0.3
HIV status unknown	1800	30.9	41.4	7.5	14.1	4.8	1.2
Overall	3318	34.5	40.1	7.5	12.9	4.1	0.9

7.4 DISCUSSION

Amongst women of reproductive age, the percentage of deaths attributed to HIV/AIDS-related conditions varied from 33.8% using InterVA-4 up to 74.9% through the Lopman algorithm. We have no gold standard for identifying HIV/AIDS-related deaths in the ALPHA data, so it is not possible to know the true percentage, but an obvious difference between the two methods is the specificity ascertained using a recent HIV negative test result as the gold standard. This was 63.9% for the Lopman algorithm and 82.7% for InterVA-4. Further exploration suggested that the levels of specificity observed are unlikely to lead to major discrepancies between the actual and the estimated percentage of deaths attributable to HIV/AIDS, given the high prevalence of HIV among the women who died.

It was not possible to measure sensitivity due to the lack of a gold standard; however, the percentage of HIV-infected deaths attributed to HIV/AIDS-related conditions by InterVA-4 was considerably lower than the percentage of deaths attributed to HIV/AIDS based on the attributable fractions obtained from the differences in mortality rates in HIV-infected and uninfected women (93.0%). Including deaths attributed to TB substantially increased the estimates from InterVA-4, particularly in uMkhanyakude, resulting in similar estimates of HIV/AIDS-related mortality to those from the Lopman algorithm. The difficulties in teasing out TB deaths from HIV/AIDS-related deaths is well recognised with numerous studies showing that the sensitivity of InterVA-4 can be improved, with little impact on specificity, by grouping HIV/AIDS and TB deaths.(90, 239, 240)

On the other hand, the relatively high estimate based on the Lopman algorithm could be due, in part, to the definition of an HIV/AIDS-related death which was used as the gold standard to develop this algorithm. An HIV/AIDS-related death was defined as a death to an HIV-infected individual, excluding injury or direct obstetric deaths. This is likely to more accurately reflect HIV/AIDS-related deaths in the pre-ART era when such deaths dominated the mortality profile of HIV-infected individuals. However, with the introduction of ART dramatic decreases have been seen in AIDS-related mortality rates in HIV-infected individuals,(77) with increases in the likelihood of other causes of death.(241) Therefore, the algorithm is probably closer to identifying deaths “with HIV” rather than “from HIV” for deaths occurring since ART became available.

There was extensive between-site variation in the percentage of deaths attributed to HIV/AIDS-related causes at the population level and amongst HIV-infected women using both the Lopman algorithm and InterVA-4. Knowing the extent to which this reflects actual differences in the CSMFs is difficult to quantify as levels of misclassification also appeared to vary between sites. The specificity of the Lopman algorithm, for example, varied from 59.1% in Kisesa to 75.0% in Karonga. Discrepancy in the between-site trends in the attributable risk percentage (AR%) and estimates of the percentage of HIV/AIDS-related deaths amongst the HIV-infected deaths suggests there may also be misclassification amongst HIV-infected women. According to the AR%, Karonga has the highest HIV attributable mortality, while it is in uMkhanyakude that we see the highest percentage of deaths that are attributed as HIV/AIDS-related according to the Lopman algorithm. It is also plausible, however, that this discrepancy is explained by differences in the prevalence of diseases which HIV increases the risk of, but which are not classified as HIV/AIDS-related, between the different settings.

Overall, a substantially lower percentage of deaths were attributed to HIV/AIDS amongst pregnant and postpartum women. This was particularly the case using the Lopman algorithm where 29.9% of pregnancy-related deaths and 77.3% of deaths outside the pregnancy period were estimated to be HIV/AIDS-related. It is unsurprising that a lower percentage of deaths would be attributed to HIV/AIDS amongst pregnant and postpartum women, given the lower prevalence of HIV in pregnant women and the lower percentage of deaths which are HIV-infected in pregnant and postpartum women compared with non-pregnant women (40.3% versus 23.7%). It is also likely that differential misclassification of the algorithms led to some of the observed difference, with the specificity of both methods much higher in pregnant than non-pregnant women. However, even when restricting just to the sample of HIV-infected deaths, estimates of the percentage of deaths attributable to HIV/AIDS remained higher in non-pregnant and postpartum women. This is likely to be explained in part by the ‘healthy pregnant woman effect’(124) i.e. women who are at an advanced stage of HIV/AIDS are much less likely to become pregnant.

The percentage of pregnancy-related deaths attributed to HIV/AIDS in this study is much higher than the pooled estimate from the systematic review by Grollman and Ronsmans of only 3.4%.(27) The highest individual study estimate from the review was 27%,(205) but the majority of the studies (13/19) reported a percentage of 5% or lower. Most of the papers included in the systematic review used physician review as opposed to automated methods, which may account for some of the discrepancy. In

the absence of physician review data for the ALPHA sites it was not possible to test this; however, a study using data from Karonga, Malawi actually found that InterVA-4 was less likely to code deaths to those aged 15-59 years as HIV/AIDS-related compared to physicians.(90)

The ALPHA data provided a unique opportunity to explore the validity of two different automated methods in identifying HIV/AIDS methods when the HIV status is known. However, there are a number of limitations to the data, which need to be considered when interpreting the results. Firstly, there were extensive amounts of missing symptom data. It was not possible to restrict the analysis to only complete cases, due to variation between the sites in the exact data collected. Therefore missing data was effectively treated as a symptom being reported not to have occurred. Secondly, there were only a small number of deaths, which limited our ability to conduct stratified analyses. In particular, there were only a small number of pregnancy-related deaths, necessitating a pooled analysis across the sites. The pooled analyses should be interpreted with caution, with results generally being driven by uMkhanyakude which has far more deaths than either of the other sites. Thirdly, it is likely that ART will change both the percentage of deaths attributable to HIV/AIDS and the presentation of HIV/AIDS-related conditions; unfortunately, it was not possible to assess whether the validity of the methods varied with ART use, as data on individual level ART use was not available. However, should this data have been available we would have only been able to stratify our results by ART status as neither method explored in this chapter takes into account whether someone was on ART or not in assigning cause of death.

The aim of this chapter was to assess the validity of the Lopman algorithm and InterVA-4 in assigning HIV/AIDS deaths by pregnancy status. We observe variability in the percentage of deaths attributed to HIV/AIDS-related causes by site and pregnancy status, but unfortunately variability in levels of misclassification between different subgroups (i.e. by pregnancy status and/or study site) limits the ability of such tools to provide comparable estimates of the percentage of deaths due to HIV/AIDS. Ideally, the CSMF should be adjusted to account for such differential levels of misclassification. This, however, will require a gold standard, such as cause of death from an autopsy, which was not available in this study. Without such adjustment for misclassification, it will be difficult to draw conclusions about differences in CSMFs observed from VA data between pregnant and non-pregnant women. More generally, this work highlights the difficulties in identifying HIV/AIDS-related deaths using VA data. The two different methods appear to show similar relative patterns in HIV/AIDS-related mortality (e.g.

highest in uMkhanyakude, higher in non-pregnant than pregnant women) but are different with respect to the magnitude of the percentage of deaths attributed to HIV/AIDS-related conditions.

8 DISCUSSION

The overall aim of this thesis was to investigate the contribution of HIV to mortality during the pregnancy and postpartum period. The following research questions were addressed:

1. What is the excess mortality associated with HIV amongst pregnant and postpartum women?

2. Is there evidence for an interaction between HIV and pregnancy?
    a. Does HIV increase the risk of obstetric complications?
    b. Does pregnancy accelerate HIV disease progression?

This chapter is divided into two main sections. In the first I will briefly synthesise the key findings from the more extensive discussions included within each results chapter and assess whether we can distinguish indirect and coincidental deaths among pregnancy-related deaths attributed to HIV. Second, I will discuss the implications of this work for public health, the measurement of maternal mortality and for future research.

8.1 SUMMARY OF FINDINGS

8.1.1 What is the excess mortality attributable to HIV amongst pregnant and postpartum women?

In this thesis, two approaches to calculate the percentage of deaths attributable to HIV in pregnant and postpartum women were used. First, I calculated the population attributable fraction (PAF), where pregnancy-related mortality rates in HIV-uninfected women are compared to pregnancy-related mortality rates in all women. The PAF captures two components of mortality attributable to HIV: 1) deaths directly due to HIV/AIDS-related conditions and; 2) deaths where HIV contributed to the risk of dying but the individual died from a non-HIV/AIDS-related cause (e.g. a death due to malaria where HIV increased either the severity of, or susceptibility to, malaria). Second, I examined the percentage of deaths classified as HIV/AIDS-related using verbal autopsy (VA) data. This second approach should only capture deaths that are directly due to HIV/AIDS-related conditions. Figure 8.1 summarises the estimates of the

percentage of deaths that are HIV/AIDS-related in pregnant and postpartum women in both sub-Saharan Africa and for the ALPHA network sites, using my estimates from the PAF and VA analyses, and those from the literature.

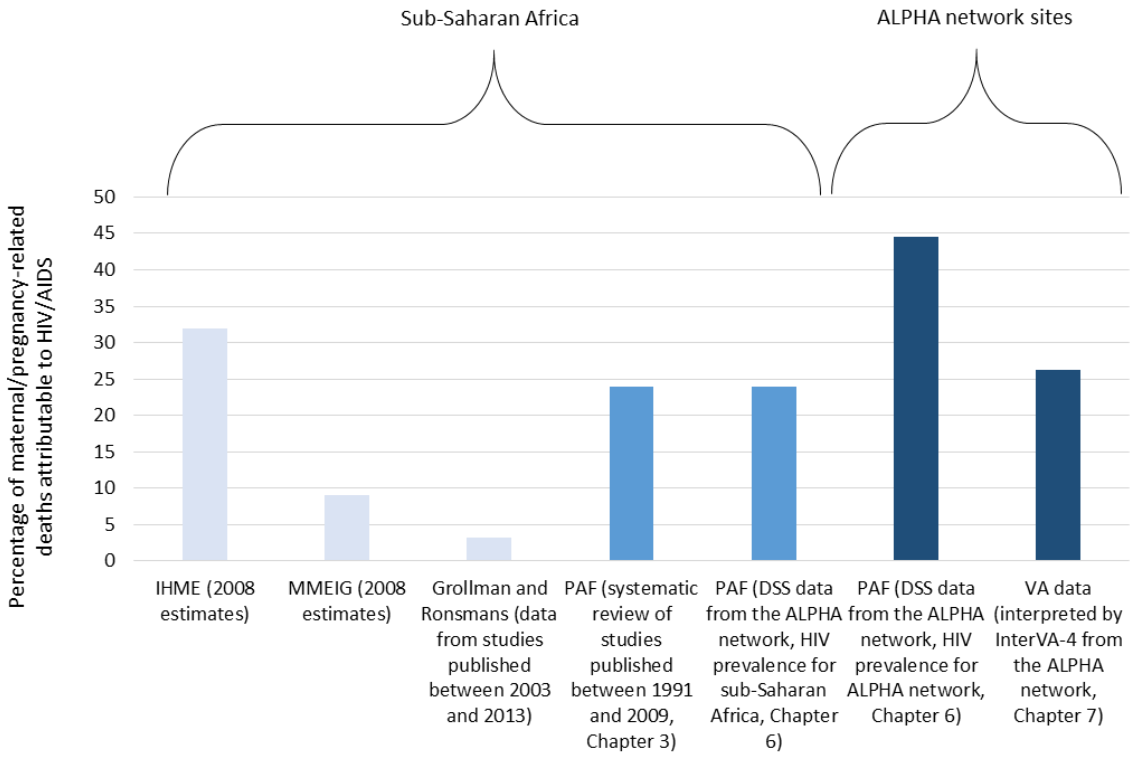

Figure 8.1: Comparison of estimates of the percentage of maternal/pregnancy-related deaths attributable to HIV/AIDS in sub-Saharan Africa.
Abbreviations: IHME=Institute of Health Metrics and Evaluation; MMEIG=Maternal Mortality Estimation Interagency Group; PAF=Population Attributable Fraction; DSS= Demographic Surveillance Site; VA= Verbal Autopsy

Using the PAF, 24% of pregnancy-related deaths in sub-Saharan Africa were thought to be attributable to HIV. This estimate is much higher than the systematic review of cause of death studies by Grollman and Ronsmans where 3% of deaths in pregnant and postpartum women were classified as HIV/AIDS-related.(242)

In the ALPHA network sites, where the prevalence of HIV was higher than the average for sub-Saharan Africa, 44.6% of pregnancy-related deaths were predicted to be attributable to HIV based on the PAF. As expected, the VA data provided lower estimates of the percentage of HIV/AIDS-related deaths compared with the PAF (26.3% using InterVA and combining HIV/AIDS-related and TB deaths and 29.9% using the Lopman algorithm). Even though the VA interpretation methods have low specificity in identifying HIV/AIDS-related deaths, I found that the levels of specificity observed using the current ALPHA data are unlikely to lead to substantial

overestimates of the percentage of deaths classified as HIV/AIDS-related given the high levels of HIV/AIDS-related deaths in the population; however, as the percentage of HIV/AIDS-related deaths reduces with wider availability of ART, even small deviations from 100% specificity may lead to substantial overestimates of HIV/AIDS-related deaths using VAs.

8.1.2 Is there any evidence for an interaction between HIV and pregnancy?

In the systematic review comparing the risk of obstetric complications in HIV-infected and uninfected women I found that HIV increases the risk of intrauterine infections (including sepsis and endometritis) during pregnancy, labour and after delivery but the effect of HIV on obstetric haemorrhage, hypertensive disorders of pregnancy and dystocia was weak and inconsistent.(125)

In the second systematic review, I found that there was no evidence of an association between pregnancy and progression to HIV/AIDS-defining illnesses, drop in CD4 count or death in settings where ART was available. In the absence of ART, there appear to be small but appreciable increases in the risk of several negative HIV outcomes with pregnancy, but the small number of studies made it impossible to draw firm conclusions. Caution needs to be taken in interpreting these results, however, as the quality of the studies was poor and few studies conceptualised why or for how long pregnancy may accelerate HIV disease progression.

The evidence from these reviews, limited as they may be, suggests that most of the excess pregnancy-related mortality attributable to HIV is likely to be coincidental to the pregnancy. The higher risk of intrauterine infections is clinically meaningful – and biologically plausible – but intrauterine infections make up a relatively small proportion of deaths in HIV-infected pregnant women.(178) Where ART is available, almost all deaths attributable to HIV in pregnant and postpartum women are likely to be coincidental to the pregnancy. The issue is more complicated where ART is unavailable. In these settings, we do see small increases in the risk of HIV disease progression with pregnancy, but the confidence intervals are wide and based on these alone we would have to conclude that there is no evidence of an association. However, all but one study report relative risks consistent with an excess risk with pregnancy. If we assume that this increased risk is real then we can extrapolate to calculate the percentage of HIV/AIDS-related deaths which should be classified as indirect maternal deaths. For example, based on three studies, we find that the risk of an HIV-related

death is 1.35 times higher in pregnant compared to non-pregnant women; we can therefore predict that approximately 25% of HIV/AIDS-related deaths were aggravated by pregnancy and should be classified as indirect (i.e. out of 135 deaths to pregnant and postpartum women, 35 will have been aggravated by pregnancy).

8.1.3 Can we distinguish indirect and coincidental deaths among pregnancy-related deaths attributed to HIV?

Distinguishing between indirect and coincidental HIV/AIDS-related deaths requires information on whether the pregnancy aggravated HIV disease progression; however there are no particular symptoms associated with accelerated HIV disease progression. Therefore, in practice, it is unclear how we can distinguish whether HIV was aggravated by pregnancy, even in settings where good clinical data and information on the HIV status of the deceased are available. It is even more difficult to see how it would be possible to assess whether an HIV/AIDS-related death was aggravated by pregnancy in settings where cause of death assignment relies on VA, given the difficulties in simply identifying HIV/AIDS-related deaths.

8.2 RECOMMENDATIONS

The findings of this thesis have important implications for public health interventions, the measurement of maternal mortality and future research priorities.

8.2.1 Public Health

Several public health recommendations, spanning counselling for HIV-infected non-pregnant women on their reproductive choices and for the care of HIV-infected pregnant women, can be made based on the work presented in this thesis.

On balance, there appears to be little evidence for an interaction between HIV and pregnancy in settings where ART is available, implying that that there is little reason for health professionals to discourage healthy, HIV-infected women from becoming pregnant if they wish to do so. This recommendation is made assuming adequate counselling is available on how to prevent transmission to both her partner and baby, and that a number of interventions are available to minimise the risk of mortality, as outlined below.

Taking precautions to reduce the risk of intrauterine infections in HIV-infected women is important. HIV-infected women should have access to prophylactic antibiotics to minimise the risk of intrauterine infections(243) and procedures which independently increase the risk of sepsis should be avoided where possible. For example, caesarean sections are known to be associated with increased risk of intrauterine infections,(244) a risk which is likely to be exacerbated in sub-Saharan Africa.(245) In cases where the woman has a high viral load, and is therefore at increased risk of transmitting HIV to her child, a caesarean may be necessary; otherwise caesareans should be avoided in HIV-infected women.

Given that most excess HIV/AIDS-related mortality is coincidental to pregnancy, the biggest impact on reducing HIV-related mortality in pregnant and postpartum women will require that HIV-infected pregnant women receive timely access to ART. I therefore recommend that the remit of safe motherhood programmes should be extended to the provision of ART. Integration of maternal health and HIV service is likely to overcome a number of barriers to seeking ART including transportation costs, time off work and issues surrounding stigma.(246) A recent systematic review found that the percentage of women enrolled in ART was double in antenatal care (ANC) clinics with integrated ART compared to woman attending ANC clinics not providing ART.(246) However, while there appear to be benefits to integrating maternal and HIV services, the best way to achieve such integration is not well documented.(247) In particular, studies are required to assess what the possible implications of integrating services are on staff workload and service quality.

One of the proposed strategies to integrate maternal health service delivery and HIV services is by introducing Option B+, where all HIV-infected pregnant woman are eligible for lifelong ART.(248) This facilitates integration of ART provision into maternal health services by removing the need to perform $CD4^+$ T-lymphocyte counts as required by alternative WHO recommended regimens.(249) Preliminary evidence suggests that this approach has been effective in increasing the number of pregnant and postpartum women on ART. In Malawi, where Option B+ was first rolled out, a seven-fold increase in pregnant and postpartum women on ART was observed during the first year of implementation.(250) However, some researchers have urged caution in the adoption of the Option B+ strategy, raising concerns about poor ART adherence amongst HIV-infected women who feel healthy, the possible long term effects of being on ART and cost-effectiveness.(176, 251) Some worrying results from Malawi suggest that 17% of women starting ART under Option B+ were lost to follow-up within six

months.(252) Data from Karonga, Malawi showed that 43% of HIV-infected pregnant women not already on ART did not start ART during pregnancy or delivery, and 45% of HIV-infected women were referred to separate HIV services rather than receiving ART through ANC.(253) Ensuring that all HIV-infected pregnant and postpartum women who need ART receive and adhere to it will require further research on the barriers to accessing ART. In particular, we need to understand why some pregnant women never make it to ANC or undertake HIV testing, a recommendation noted in a recent systematic review exploring the barriers for ART in HIV-infected pregnant and postpartum women.(254)

There is scant evidence on the potential negative side effects of ART for pregnant or postpartum women and their babies. Early evidence from observational studies suggests that ART in pregnancy does not increase the risk of congenital abnormalities but may increase the risk of preterm birth and both maternal and infant anaemia.(255) We therefore echo a call made by WHO for studies to closely monitor pregnant woman on ART for potential harmful side effects for either mother or baby.(174)

8.2.2 Measurement and modelling of all-cause and HIV-related mortality in pregnant and postpartum women

The interpretation of whether HIV/AIDS-related deaths are indirectly related or coincidental to pregnancy substantially affects the reported levels of maternal mortality (which only include direct obstetric and indirect cause of death), and therefore the evaluation of safe motherhood programmes and maternal health services. If most HIV-related deaths are coincidental to pregnancy in the era of ART, then strictly speaking all HIV/AIDS-related deaths should be excluded from maternal mortality estimates. I would, however, argue that we should use pregnancy-related mortality rather than maternal mortality for monitoring progress towards reducing mortality in pregnancy and the postpartum, for two main reasons. Firstly, given that HIV-related deaths during pregnancy or the postpartum may be preventable with timely access to ART in the prenatal period, it is important to monitor the number of these deaths. Secondly, as it is not possible to distinguish indirect and coincidental HIV/AIDS-related deaths the entire concept of maternal death could be called into question. The difficulties in identifying causes of death aggravated by pregnancy have also been identified for other causes (e.g. malaria) and supports simplification in the methods used to monitor deaths in pregnant and postpartum women.(205)

The findings in this thesis have prompted IHME and MMEIG to alter their model assumptions with dramatic consequences for the percentage of maternal deaths attributed to HIV. Compared with previous IHME models,(28, 29) outlined in Section 1.2.2, the most recent model from IHME (30) took a very different approach for dealing with HIV/AIDS-related deaths, incorporating methods presented in this thesis. On updating the review presented in Chapter 3 they found that HIV-infected women had 6.4 times the risk of pregnancy-related mortality compared with uninfected women. The change in the pooled RR from 7.7 to 6.4 was driven by the exclusion of three studies, including one which recruited women at high risk of mortality. Using this RR and data on HIV prevalence in pregnant women from the UNAIDS Spectrum database they calculated country, year and age-specific PAFs. The total number of HIV/AIDS-related deaths were calculated by applying these PAFs to the estimated number of maternal deaths produced from a cause of death ensemble model. To assess how many of these HIV-related deaths should be considered maternal, a systematic review comparing mortality in HIV-infected pregnant and non-pregnant women was conducted: based on only two studies,(190, 191) they found that HIV-infected pregnant women have 13% higher risk of death than HIV-infected non-pregnant women (95% CI: 0.73-1.77). They therefore conclude that 11.5% (i.e. 13% / 113%) of HIV-related deaths should be counted as maternal. Interestingly, my systematic review – which was not yet published at the time – found nine studies comparing mortality in HIV-infected pregnant and non-pregnant women.

In the MMEIG model (7) several key parameters for the estimation of the number of HIV/AIDS-related maternal deaths were adapted from the earlier models,(31, 32) described in Section 1.2.2, based on data from the ALPHA network. Firstly, to calculate the proportion of AIDS deaths in women that occur during pregnancy or postpartum, an estimate of the relative risk of dying from AIDS for a pregnant versus a non-pregnant woman is required. This proportion was previously set to be 0.4 based on a statistical analysis of deviance scores, but was reduced to 0.3 from the mortality rates underpinning the results presented in Chapter 6 (pregnant and postpartum women: 3.43 per 1,000 person-years, not pregnant or postpartum women 11.50 per 1,000 person-years). The MMEIG model also requires a measure of the “fraction of AIDS deaths among pregnant women that qualify as maternal because of some causal relationship with the pregnancy, delivery or postpartum period”. In the absence of empirical data this was previously set to 0.5, but was reduced to 0.3, “in light of new data from the network for Analysing Longitudinal Population-based HIV/AIDS data on Africa”.(7) From the MMEIG report it is not possible to see how this value of 0.3 was

reached, and based on my assessment of the ALPHA VA data I would argue that it is not possible to ascertain the fraction of HIV/AIDS-related deaths aggravated by pregnancy.

The drop in the percentage of maternal deaths attributable to HIV/AIDS from 9.0% in 2008 to 3.8% in 2013 in the MMEIG models and from 32% in 2008 to 1.5% in 2013 in the IHME models are likely to principally reflect changes in the model assumptions. These changes to the models have been driven by not being able to accurately estimate which HIV-related deaths should be classified as indirect or coincidental to pregnancy, and will undoubtedly change as more evidence becomes available. The utility of results which are so sensitive to model assumptions is questionable, and provide further support for using pregnancy-related mortality rather than maternal mortality which would negate the need to make such assumptions.

Prioritising interventions to prevent deaths in pregnant and postpartum women requires information not only on the levels of pregnancy-related mortality but also on the causes of death. The difficulties in identifying HIV/AIDS-related deaths using VA data interpreted with automated methods have been illustrated in this thesis. Unfortunately, physician review data were not available but in a recent PhD thesis using data from Kisesa, Tanzania it was found that, at 88.3%, physician review had higher specificity in identifying HIV/AIDS-related deaths than either InterVA-4 (81.4%) or the Lopman algorithm (66.0%).(256) To accurately ascertain causes of death in pregnant and postpartum women clearly requires more precise methods. Ideally data would be available on the HIV status of the deceased, but this is unrealistic in the near future. New simplified methods for collecting cause of death data in resource poor settings are required, and investigations are currently underway to assess whether minimally invasive autopsies are feasible and acceptable.(257) Until other methods are available, we should strive to improve the quality of VAs and to understand the pitfalls of current methods of interpreting the data and the effects these may have on the estimated cause-specific mortality fractions (CSMF). Estimates produced from VAs are likely to remain imprecise, and great caution should be taken if trying to compare CSMFs over time or in different places, given that the extent to which imprecise tools provide incorrect estimates will vary depending on the true percentage of deaths attributable to the cause in the population.

8.2.3 Future research

This thesis used empirical data to determine the contribution of HIV to pregnancy-related mortality, overcoming issues with previous modelled estimates which relied heavily on assumptions on the extent to which pregnancy aggravates HIV. The two data sources (published literature and DSS data from the ALPHA network) enabled the objectives of the PhD to be addressed, but at the same time highlighted ways to improve future data collection and reporting.

The strength of the systematic reviews were their comprehensive nature, with literature identified from both high and low income settings for all three reviews. However, the quality of the studies was generally judged to be poor, suggesting that improvements can be made to data collection and analyses. One of the main criticisms of the studies comparing the risk of mortality and obstetric complications in HIV-infected and HIV-uninfected pregnant and postpartum women was that very few adjusted for confounders. Key confounders which should be considered by future studies include age and socio-economic status, which are known to be associated with HIV status and independently associated with the risk of mortality and complications of pregnancy. Adjusted relative risks were more commonly presented in the studies which compared HIV disease progression in pregnant and non-pregnant woman; however, as discussed in detail in Chapter 5, studies varied extensively in the methods used to account for differences in HIV stage between pregnant and non-pregnant women. To compare disease progression in pregnant and non-pregnant women future studies must collect detailed information on CD4 cell percentage at fixed follow-up points so that the "healthy pregnant women effect" can be accounted for**.** Studies should avoid using data on absolute CD4 cell count, as haemodilution associated with pregnancy results in lower CD4 cell counts amongst pregnant women compared with non-pregnant women at the same stage of clinical HIV disease.(196)

The ALPHA data provided a unique opportunity to explore the impact of HIV on pregnancy-related mortality using population-based data from sub-Saharan Africa. Having access to data from multiple sites enabled us to pool the data and therefore increase the sample size for analyses. The pooled data set comprised over 600,000 person-years amongst women of reproductive age with nearly 87,000 observed pregnancies, much larger than most studies from sub-Saharan Africa. However, the pregnancy-related mortality rates were unexpectedly low in some of the sites, suggesting that some women who were pregnant or postpartum were being incorrectly

misclassified as non-pregnant. None of the sites were set up to monitor pregnancy-related mortality, therefore it is unsurprising that some of these deaths would be missed. Across the six sites which contributed data to this thesis, only half collected information on stillbirths and only four collected pregnancy report data. Furthermore, in three of the sites there were long intervals (> 1 year) between DSS data collection rounds. It can be recommended that sites collect information on pregnancy status, and whether there was a stillbirth to minimise the chances of misclassifying a woman as non-pregnant. The usefulness of pregnancy reports can also be increased by collecting data on the gestational age at the report at the time of the pregnancy report. For those sites which have long intervals between DSS rounds, additional systems (e.g. key informants) should be considered to report births.

Using data from both the systematic review and ALPHA network sites, I attempted to examine the impact of ART on the effect of HIV on pregnancy-related mortality; however, these analyses were limited by the lack of individual level ART data. A clear priority for future research is therefore understanding which ART and PMTCT programmes are most successful in bringing down pregnancy-related mortality by using individual-level data on ART use.

To conclude, the results from this thesis provide a unique insight into the contribution of HIV to mortality in pregnant and postpartum women. We have shown that HIV is an important cause of pregnancy-related mortality, but suggested that most of these HIV-related deaths are coincidental to the pregnancy. These results have implications for HIV-infected women, the measurement of maternal mortality and future research. In particular, the results of this thesis imply that there is little reason to discourage healthy, HIV-infected women with access to ART from becoming pregnant if they wish to do so.

9 REFERENCES

1. World Health Organization. Global HIV/AIDS Response: Epidemic update and health sector progress towards Universal Access. 2011.
2. Department of Health (Republic of South Africa). The 2010 National Antenatal Sentinal HIV and Syphilis Prevalence Survey in South Africa. 2011.
3. Zimbabwe Goverment. Global AIDS Response Progress Report 2012: Follow-up to the 2011 Political Declaration on HIV/AIDS Intensifying out Efforts to Eliminate HIV/AIDS. 2012.
4. Malawi Government. 2012 Global AIDS Response Progress Report: Malawi Country Report for 2010 and 2011. 2012.
5. McIntyre J. Mothers infected with HIV. British Medical Bulletin. 2003;67(1):127-35.
6. Graham W, Hussein J. Measuring and estimating maternal mortality in the era of HIV/AIDS. Workshop on HIV/AIDS and Adult mortality in developing countries; New York: Population Division; 2003.
7. World Health Organization. Trends in Maternal Mortality: 1990 to 2013. World Health Organization; 2014.
8. Fawcus SR, van Coeverden de Groot HA, Isaacs S. A 50-year audit of maternal mortality in the Peninsula Maternal and Neonatal Service, Cape Town (1953-2002). Bjog. 2005;112(9):1257-63.
9. Colbourn T, Lewycka S, Nambiar B, Anwar I, Phoya A, Mhango C. Maternal mortality in Malawi, 1977–2012. BMJ Open. 2013;3(12).
10. Bicego G, Boerma JT, Ronsmans C. The effect of AIDS on maternal mortality in Malawi and Zimbabwe. AIDS. 2002;16(7):1078-81.
11. World Health Organization. International Classification of Disease (ICD) [cited 2012 14/05/2012]. Available from: http://www.who.int/classifications/icd/en/index.html.
12. Salanave B, Bouvier-Colle MH, Varnoux N, Alexander S, Macfarlane A. Classification differences and maternal mortality: a European study. MOMS Group. MOthers' Mortality and Severe morbidity. International Journal of Epidemiology. 1999;28(1):64-9.
13. Department of Health. Why mothers die: report on confidential enquiries into maternal deaths in the United Kingdom 1994-1996. The Stationary Office, 1998.
14. Ronsmans C, Khlat M. Adolescence and risk of violent death during pregnancy in Matlab, Bangladesh. Lancet. 1999;354(9188):1448.
15. Dannenberg AL, Carter DM, Lawson HW, Ashton DM, Dorfman SF, Graham EH. Homicide and other injuries as causes of maternal death in New York City, 1987 through 1991. American Journal of Obstetrics and Gynecology. 1995;172(5):1557-64.
16. World Health Organization. The WHO application of ICD-10 to deaths during pregnancy, childbirth and the puerperium: ICD-MM. World Health Organization; 2012.
17. Rosen JE, de Zoysa I, Dehne K, Mangiaterra V, Abdool-Karim Q. Understanding Methods for Estimating HIV-Associated Maternal Mortality. J Pregnancy. 2012;2012:958262.
18. Kongnyuy EJ, Mlava G, van den Broek N. Facility-based maternal death review in three districts in the central region of Malawi: an analysis of causes and characteristics of maternal deaths. Womens Health Issues. 2009;19(1):14-20.
19. van Dillen J, Meguid T, van Roosmalen J. Maternal mortality audit in a hospital in Northern Namibia: the impact of HIV/AIDS. Acta Obstet Gynecol Scand. 2006;85(4):499-500.
20. Black V, Brooke S, Chersich MF. Effect of human immunodeficiency virus treatment on maternal mortality at a tertiary center in South Africa: a 5-year audit. Obstet Gynecol. 2009;114(2 Pt 1):292-9.

21. Buchmann EJ, Mnyani CN, Frank KA, Chersich MF, McIntyre JA. Declining maternal mortality in the face of persistently high HIV prevalence in a middle-income country. BJOG: An International Journal of Obstetrics & Gynaecology. 2014:n/a-n/a.
22. Byass P, de Courten M, Graham WJ, Laflamme L, McCaw-Binns A, Sankoh OA, et al. Reflections on the Global Burden of Disease 2010 Estimates. PLoS Med. 2013;10(7):e1001477.
23. Fottrell E, Byass P. Verbal Autopsy: Methods in Transition. Epidemiologic Reviews. 2010;32(1):38-55.
24. Soleman N, Chandramohan D, Shibuya K. Verbal autopsy: current practices and challenges. Bull World Health Organ. 2006;84(3):239-45.
25. KAMALI A, WAGNER H-U, NAKIYINGI J, SABIITI I, KENGEYA-KAYONDO JF, MULDER DW. Verbal Autopsy as a Tool for Diagnosing HIV-Related Adult Deaths in Rural Uganda. International Journal of Epidemiology. 1996;25(3):679-84.
26. Byass P, Calvert C, Miiro-Nakiyingi J, Lutalo T, Michael D, Crampin A, et al. InterVA-4 as a public health tool for measuring HIV/AIDS mortality: a validation study from five African countries. Glob Health Action. 2013;6:22448.
27. Grollman C, Ronsmans C. Systematic review of the proportion of pregnancy-related deaths attributed to HIV in population-based studies in sub-Saharan Africa. Trop Med Int Health. 2014;19(1):83-97.
28. Hogan MC, Foreman KJ, Naghavi M, Ahn SY, Wang M, Makela SM, et al. Maternal mortality for 181 countries, 1980-2008: a systematic analysis of progress towards Millennium Development Goal 5. Lancet. 2010;375(9726):1609-23.
29. Lozano R, Wang H, Foreman KJ, Rajaratnam JK, Naghavi M, Marcus JR, et al. Progress towards Millennium Development Goals 4 and 5 on maternal and child mortality: an updated systematic analysis. The Lancet. 2011;378(9797):1139-65.
30. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, Shackelford KA, Steiner C, Heuton KR, et al. Global, regional, and national levels and causes of maternal mortality during 1990?2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2014;384(9947):980-1004.
31. World Health Organization. Trends in Maternal Mortality: 1990 to 2008. World Health Organization; 2010.
32. World Health Organization. Trends in maternal mortality: 1990-2012. World Health Organization; 2012.
33. Biggar RJ, Pahwa S, Minkoff H, Mendes H, Willoughby A, Landesman S, et al. Immunosuppression in pregnant women infected with human immunodeficiency virus. Am J Obstet Gynecol. 1989;161(5):1239-44.
34. Maartens G, Celum C, Lewin SR. HIV infection: epidemiology, pathogenesis, treatment, and prevention. The Lancet.384(9939):258-71.
35. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 Infection. New England Journal of Medicine. 2011;364(20):1943-54.
36. Luckheeram RV, Zhou R, Verma AD, Xia B. CD4+T Cells: Differentiation and Functions. Clinical and Developmental Immunology. 2012;2012:12.
37. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and Infection. New England Journal of Medicine. 2014;370(23):2211-8.
38. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis. 2006;12(11):1638-43.
39. Zoller AL, Schnell FJ, Kersh GJ. Murine pregnancy leads to reduced proliferation of maternal thymocytes and decreased thymic emigration. Immunology. 2007;121(2):207-15.
40. Elenkov IJ, Wilder RL, Bakalov VK, Link AA, Dimitrov MA, Fisher S, et al. IL-12, TNF-alpha, and hormonal changes during late pregnancy and early postpartum: implications for autoimmune disease activity during these times. J Clin Endocrinol Metab. 2001;86(10):4933-8.
41. Runmarker B, Andersen O. Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis. Brain. 1995;118 (Pt 1):253-61.

42. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. Jama. 2010;303(15):1517-25.
43. Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. Am J Obstet Gynecol. 2011;205(1):10-8.
44. Aggarwal R, Krawczynski K. Hepatitis E: an overview and recent advances in clinical and laboratory research. J Gastroenterol Hepatol. 2000;15(1):9-20.
45. Kang AH, Graves CR. Herpes simplex hepatitis in pregnancy: a case report and review of the literature. Obstet Gynecol Surv. 1999;54(7):463-8.
46. Heffron R, Donnell D, Kiarie J, Rees H, Ngure K, Mugo N, et al. A prospective study of the effect of pregnancy on CD4 counts and plasma HIV-1 RNA concentrations of antiretroviral-naive HIV-1-infected women. J Acquir Immune Defic Syndr. 2014;65(2):231-6.
47. Van der Paal L, Shafer LA, Mayanja BN, Whitworth JA, Grosskurth H. Effect of pregnancy on HIV disease progression and survival among women in rural Uganda. Tropical Medicine and International Health. 2007;12(8):920-8.
48. Brettle RP, Raab GM, Ross A, Fielding KL, Gore SM, Bird AG. HIV infection in women: immunological markers and the influence of pregnancy. Aids. 1995;9(10):1177-84.
49. Temmerman M, Nagelkerke N, Bwayo J, Chomba EN, Ndinya-Achola J, Piot P. HIV-1 and immunological changes during pregnancy: a comparison between HIV-1-seropositive and HIV-1-seronegative women in Nairobi, Kenya. Aids. 1995;9(9):1057-60.
50. Vimercati A, Greco P, Lopalco PL, Loverro G, Fiore JR, Bettocchi S, et al. Immunological markers in HIV-infected pregnant and non-pregnant women. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2000;90(1):37-41.
51. French R, Brocklehurst P. The effect of pregnancy on survival in women infected with HIV a systematic review of the literature and meta-analysis. BJOG: An International Journal of Obstetrics & Gynaecology. 1998;105(8):827-35.
52. Deschamps MM, Fitzgerald DW, Pape JW, Johnson WD, Jr. HIV infection in Haiti: natural history and disease progression. Aids. 2000;14(16):2515-21.
53. Gray RH, Li X, Kigozi G, Serwadda D, Brahmbhatt H, Wabwire-Mangen F, et al. Increased risk of incident HIV during pregnancy in Rakai, Uganda: a prospective study. The Lancet.366(9492):1182-8.
54. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. PLoS Med. 2014;11(2):e1001608.
55. Marston M, Newell ML, Crampin A, Lutalo T, Musoke R, Gregson S, et al. Is the risk of HIV acquisition increased during and immediately after pregnancy? A secondary analysis of pooled HIV community-based studies from the ALPHA network. PLoS One. 2013;8(12):e82219.
56. Montgomery K. Childbirth Education for the HIV-Positive Woman. J Perinat Educ. 2003;12(4):16-26.
57. Turan JM, Bukusi EA, Cohen CR, Sande J, Miller S. Effects of HIV/AIDS on Maternity Care Providers in Kenya. Journal of Obstetric, Gynecologic, & Neonatal Nursing. 2008;37(5):588-95.
58. Awiti Ujiji O, Ekstrom AM, Ilako F, Indalo D, Wamalwa D, Rubenson B. Reasoning and deciding PMTCT-adherence during pregnancy among women living with HIV in Kenya. Cult Health Sex. 2011;13(7):829-40.
59. Leroy V, Ladner J, Nyiraziraje M, De Clercq A, Bazubagira A, Van de Perre P, et al. Effect of HIV-1 infection on pregnancy outcome in women in Kigali, Rwanda, 1992-1994. Pregnancy and HIV Study Group. AIDS. 1998;12(6):643-50.

60. Minkoff HL, Henderson C, Mendez H, Gail MH, Holman S, Willoughby A, et al. Pregnancy outcomes among mothers infected with human immunodeficiency virus and uninfected control subjects. Am J Obstet Gynecol. 1990;163(5 Pt 1):1598-604.
61. Azria E, Kane A, Tsatsaris V, Schmitz T, Launay O, Goffinet F. Term labor management and outcomes in treated HIV-infected women without contraindications to vaginal delivery and matched controls. Int J Gynaecol Obstet. 2010;111(2):161-4.
62. Conde-Agudelo A, Villar J, Lindheimer M. Maternal infection and risk of preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol. 2008;198(1):7-22.
63. Bodkin C, Klopper H, Langley G. A comparison of HIV positive and negative pregnant women at a public sector hospital in South Africa. J Clin Nurs. 2006;15(6):735-41.
64. Frank KA, Buchmann EJ, Schackis RC. Does human immunodeficiency virus infection protect against preeclampsia-eclampsia? Obstet Gynecol. 2004;104(2):238-42.
65. Maiques-Montesinos V, Cervera-Sanchez J, Bellver-Pradas J, Abad-Carrascosa A, Serra-Serra V. Post-cesarean section morbidity in HIV-positive women. Acta Obstet Gynecol Scand. 1999;78(9):789-92.
66. Semprini AE, Castagna C, Ravizza M, Fiore S, Savasi V, Muggiasca ML, et al. The incidence of complications after caesarean section in 156 HIV-positive women. AIDS. 1995;9(8):913-7.
67. Sekirime WK, Lule JC. Maternal morbidity following emergency caesarean section in asymptomatic HIV-1 infected patients in Mulago Hospital Kampala, Uganda. J Obstet Gynaecol. 2008;28(7):703-9.
68. van Eijk AM, Ayisi JG, ter Kuile FO, Misore AO, Otieno JA, Rosen DH, et al. HIV increases the risk of malaria in women of all gravidities in Kisumu, Kenya. AIDS. 2003;17(4):595-603.
69. Verhoeff FH, Brabin BJ, Hart CA, Chimsuku L, Kazembe P, Broadhead RL. Increased prevalence of malaria in HIV-infected pregnant women and its implications for malaria control. Trop Med Int Health. 1999;4(1):5-12.
70. Whitworth J, Morgan D, Quigley M, Smith A, Mayanja B, Eotu H, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. Lancet. 2000;356(9235):1051-6.
71. Steketee RW, Wirima JJ, Bloland PB, Chilima B, Mermin JH, Chitsulo L, et al. Impairment of a pregnant woman's acquired ability to limit Plasmodium falciparum by infection with human immunodeficiency virus type-1. Am J Trop Med Hyg. 1996;55(1 Suppl):42-9.
72. Dairo MD, Lawoyin TO, Onadeko MO, Asekun-Olarinmoye EO, Adeniji AO. HIV as an additional risk factors for anaemia in pregnancy: evidence from primary care level in Ibadan, Southwestern Nigeria. Afr J Med Med Sci. 2005;34(3):275-9.
73. Ticconi C, Mapfumo M, Dorrucci M, Naha N, Tarira E, Pietropolli A, et al. Effect of maternal HIV and malaria infection on pregnancy and perinatal outcome in Zimbabwe. J Acquir Immune Defic Syndr. 2003;34(3):289-94.
74. Ayisi JG, van Eijk AM, ter Kuile FO, Kolczak MS, Otieno JA, Misore AO, et al. The effect of dual infection with HIV and malaria on pregnancy outcome in western Kenya. AIDS. 2003;17(4):585-94.
75. Ford N, Calmy A, Mills EJ. The first decade of antiretroviral therapy in Africa. Global Health. 2011;7:33.
76. Herbst AJ, Mafojane T, Newell ML. Verbal autopsy-based cause-specific mortality trends in rural KwaZulu-Natal, South Africa, 2000-2009. Popul Health Metr. 2011;9:47.
77. Chihana M, Floyd S, Molesworth A, Crampin AC, Kayuni N, Price A, et al. Adult mortality and probable cause of death in rural northern Malawi in the era of HIV treatment. Trop Med Int Health. 2012;17(8):e74-83.

78. Li N, Matchi E, Spiegelman D, Chalamilla G, Hertzmank E, Sando D, et al. Maternal mortality among HIV-infected pregnant women in Tanzania. Acta Obstetricia et Gynecologica Scandinavica. 2014;93(5):463-8.
79. Liotta G, Mancinelli S, Nielsen-Saines K, Gennaro E, Scarcella P, Magid NA, et al. Reduction of Maternal Mortality with Highly Active Antiretroviral Therapy in a Large Cohort of HIV-Infected Pregnant Women in Malawi and Mozambique. PLoS ONE. 2013;8(8):e71653.
80. MacCarthy S, Laher F, Nduna M, Farlane L, Kaida A. Responding to her question: a review of the influence of pregnancy on HIV disease progression in the context of expanded access to HAART in sub-Saharan Africa. AIDS Behav. 2009;13 Suppl 1:66-71.
81. Tai JH, Udoji MA, Barkanic G, Byrne DW, Rebeiro PF, Byram BR, et al. Pregnancy and HIV disease progression during the era of highly active antiretroviral therapy. J Infect Dis. 2007;196(7):1044-52.
82. Thorne C, Newell ML. Safety of agents used to prevent mother-to-child transmission of HIV: is there any cause for concern? Drug Saf. 2007;30(3):203-13.
83. Tuomala RE, Watts DH, Li D, Vajaranant M, Pitt J, Hammill H, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. J Acquir Immune Defic Syndr. 2005;38(4):449-73.
84. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7):e1000097.
85. Stroup Df BJAMSC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. JAMA. 2000;283(15):2008-12.
86. Higgens JPT, Green S. Cochrane handbook for systematic reviews of interventions, version 5.1.0. Updated March 2011 ed: The Cochrane Collaboration 2011.
87. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.
88. Kirkwood BR, Sterne JAC. Medical Statistics. Oxford: Blackwell Science; 2003.
89. Crampin AC, Dube A, Mboma S, Price A, Chihana M, Jahn A, et al. Profile: The Karonga health and demographic surveillance system. International Journal of Epidemiology. 2012.
90. Glynn JR, Calvert C, Price A, Chihana M, Kachiwanda L, Mboma S, et al. Measuring causes of adult mortality in rural northern Malawi over a decade of change. Glob Health Action. 2014;7:23621.
91. Isingo R, Wringe A, Todd J, Urassa M, Mbata D, Maiseli G, et al. Trends in the uptake of voluntary counselling and testing for HIV in rural Tanzania in the context of the scale up of antiretroviral therapy. Trop Med Int Health. 2012;17(8):e15-25.
92. Marston M, Michael D, Wringe A, Isingo R, Clark BD, Jonas A, et al. The impact of antiretroviral therapy on adult mortality in rural Tanzania. Tropical Medicine & International Health. 2012;17(8):e58-e65.
93. Lopman B, Lewis J, Nyamukapa C, Mushati P, Chandiwana S, Gregson S. HIV incidence and poverty in Manicaland, Zimbabwe: is HIV becoming a disease of the poor? Aids. 2007;21 Suppl 7:S57-66.
94. Lopman B, Cook A, Smith J, Chawira G, Urassa M, Kumogola Y, et al. Verbal autopsy can consistently measure AIDS mortality: a validation study in Tanzania and Zimbabwe. Journal of Epidemiology and Community Health. 2010;64(4):330-4.
95. Houlihan CF, Bland RM, Mutevedzi PC, Lessells RJ, Ndirangu J, Thulare H, et al. Cohort Profile: Hlabisa HIV Treatment and Care Programme. International Journal of Epidemiology. 2011;40(2):318-26.
96. Tanser F, Hosegood V, Barnighausen T, Herbst K, Nyirenda M, Muhwava W, et al. Cohort Profile: Africa Centre Demographic Information System (ACDIS) and population-based HIV survey. Int J Epidemiol. 2008;37(5):956-62.

97. Todd J, Glynn JR, Marston M, Lutalo T, Biraro S, Mwita W, et al. Time from HIV seroconversion to death: a collaborative analysis of eight studies in six low and middle-income countries before highly active antiretroviral therapy. Aids. 2007;21 Suppl 6:S55-63.
98. Calvert C, Ronsmans C. The contribution of HIV to pregnancy-related mortality: a systematic review and meta-analysis. AIDS. 2013;27(10):1631-9
99. World Health Organization. Women and Health. 2009.
100. Mattar R, Amed AM, Lindsey PC, Sass N, Daher S. Preeclampsia and HIV infection. European Journal of Obstetrics, Gynecology and Reproductive Biology. 2004;117:240-1.
101. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: a systematic review. The Lancet. 2006;367(9516):1066-74.
102. World Health Organization. International statistical classification of diseases and related health problems, tenth revision. Vol. 1: Tabular list. Vol. 2: Instruction manual. Geneva: WHO; 2010.
103. de Groot MR, Corporaal LJ, Cronje HS, Joubert G. HIV infection in critically ill obstetrical patients. Int J Gynaecol Obstet. 2003;81(1):9-16.
104. Khan M, Pillay T, Moodley JM, Connolly CA. Maternal mortality associated with tuberculosis-HIV-1 co-infection in Durban, South Africa. AIDS. 2001;15(14):1857-63.
105. Coley JL, Msamanga GI, Fawzi MC, Kaaya S, Hertzmark E, Kapiga S, et al. The association between maternal HIV-1 infection and pregnancy outcomes in Dar es Salaam, Tanzania. BJOG. 2001;108(11):1125-33.
106. Le Coeur S, Khlat M, Halembokaka G, Augereau-Vacher C, Batala-M'Pondo G, Baty G, et al. HIV and the magnitude of pregnancy-related mortality in Pointe Noire, Congo. AIDS. 2005;19(1):69-75.
107. Ryder RW, Nsuami M, Nsa W, Kamenga M, Badi N, Utshudi M, et al. Mortality in HIV-1-seropositive women, their spouses and their newly born children during 36 months of follow-up in Kinshasa, Zaire. AIDS. 1994;8(5):667-72.
108. McDermott JM, Slutsker L, Steketee RW, Wirima JJ, Breman JG, Heymann DL. Prospective assessment of mortality among a cohort of pregnant women in rural Malawi. Am J Trop Med Hyg. 1996;55(1 Suppl):66-70.
109. Nathoo K, Rusakaniko S, Zijenah LS, Kasule J, Mahomed K, Mashu A, et al. Survival pattern among infants born to human immunodeficiency virus type-1 infected mothers and uninfected mothers in Harare, Zimbabwe. Cent Afr J Med. 2004;50(1-2):1-6.
110. Zvandasara P, Hargrove JW, Ntozini R, Chidawanyika H, Mutasa K, Iliff PJ, et al. Mortality and morbidity among postpartum HIV-positive and HIV-negative women in Zimbabwe: risk factors, causes, and impact of single-dose postpartum vitamin A supplementation. J Acquir Immune Defic Syndr. 2006;43(1):107-16.
111. Lepage P, Dabis F, Hitimana DG, Msellati P, Van Goethem C, Stevens AM, et al. Perinatal transmission of HIV-1: lack of impact of maternal HIV infection on characteristics of livebirths and on neonatal mortality in Kigali, Rwanda. AIDS. 1991;5(3):295-300.
112. Mmiro F, Ndugwa C, Guay L, Hom D, Ball P, Mugisha NK, et al. Effect of human immunodeficiency virus-1 infection on the outcome of pregnancy in Ugandan women. Pediatric AIDS and HIV Infection. 1993;4(2):67-73.
113. Nuwagaba-Biribonwoha H, Mayon-White RT, Okong P, Carpenter LM, Jenkinson C. The impact of HIV on maternal quality of life in Uganda. AIDS Care. 2006;18(6):614-20.
114. Sewankambo NK, Gray RH, Ahmad S, Serwadda D, Wabwire-Mangen F, Nalugoda F, et al. Mortality associated with HIV infection in rural Rakai District, Uganda. AIDS. 2000;14(15):2391-400.
115. Temmerman M, Chomba EN, Ndinya-Achola J, Plummer FA, Coppens M, Piot P. Maternal human immunodeficiency virus-1 infection and pregnancy outcome. Obstet Gynecol. 1994;83(4):495-501.

116. Kumar RM, Uduman SA, Khurranna AK. Impact of maternal HIV-1 infection on perinatal outcome. Int J Gynaecol Obstet. 1995;49(2):137-43.
117. Lionel J, Aleyamma TK, Varghese L, Buck J, Gopalakrishnan G, Chaguturu S, et al. HIV and obstetric complications and fetal outcomes in Vellore, India. Trop Doct. 2008;38(3):144-6.
118. Kourtis AP, Bansil P, McPheeters M, Meikle SF, Posner SF, Jamieson DJ. Hospitalizations of pregnant HIV-infected women in the USA prior to and during the era of HAART, 1994-2003. AIDS. 2006;20(14):1823-31.
119. Louis J, Landon MB, Gersnoviez RJ, Leveno KJ, Spong CY, Rouse DJ, et al. Perioperative morbidity and mortality among human immunodeficiency virus-infected women undergoing cesarean delivery. Obstetrics and Gynecology. 2007;110(2 I):385-90.
120. Figueroa-Damian R. Pregnancy outcome in women infected with the human immunodeficiency virus. . Salud publica de Mexico. 1999;41(5):362-7.
121. Chilongozi D, Wang L, Brown L, Taha T, Valentine M, Emel L, et al. Morbidity and mortality among a cohort of human immunodeficiency virus type 1-infected and uninfected pregnant women and their infants from Malawi, Zambia, and Tanzania. Pediatr Infect Dis J. 2008;27(9):808-14.
122. UNAIDS. Global Report: UNAIDS Report on the global AIDS epidemic. 2012.
123. Gray RH, Wawer MJ, Serwadda D, Sewankambo N, Li C, Wabwire-Mangen F, et al. Population-based study of fertility in women with HIV-1 infection in Uganda. The Lancet. 1998;351(9096):98-103.
124. Ronsmans C, Khlat M, Kodio B, Ba M, De Bernis L, Etard J. Evidence for a 'healthy pregnant woman effect' in Niakhar, Senegal? International Journal of Epidemiology. 2001;30(3):467-73.
125. Calvert C, Ronsmans C. HIV and the Risk of Direct Obstetric Complications: A Systematic Review and Meta-Analysis. PLoS ONE. 2013;8(10):e74848.
126. Lattof SR, Wegner MN, Langer A, the PME. Maternal Health Is Women's Health: A Call for Papers for Year 2 of the Maternal Health Task Force–PLOS Collection. PLoS Med. 2012;9(11):e1001350.
127. Abdool-Karim Q, AbouZahr C, Dehne K, Mangiaterra V, Moodley J, Rollins N, et al. HIV and maternal mortality: turning the tide. The Lancet. 2010;375(9730):1948-9.
128. Lindgren S, Martin C, Anzen B, Strand H, Bredberg-Raden U, Ehrnst A. Pattern of HIV viraemia and CD4 levels in relation to pregnancy in HIV-1 infected women. Scand J Infect Dis. 1996;28(5):425-33.
129. Rich KC, Siegel JN, Jennings C, Rydman RJ, Landay AL. CD4+ lymphocytes in perinatal human immunodeficiency virus (HIV) infection: evidence for pregnancy-induced immune depression in uninfected and HIV-infected women. J Infect Dis. 1995;172(5):1221-7.
130. Verkuyl DAA. Practising obstetrics and gynaecology in areas with a high prevalence of HIV infection. The Lancet. 1995;346(8970):293-6.
131. Berer M. HIV / AIDS, pregnancy and maternal mortality and morbidity: implications for care. Safe Motherhood initiatives: critical issues, edited by Marge Berer and TK Sundari Ravindran: Oxford, England, Blackwell Science, 1999.; 1999. p. 198-210.
132. Begg C, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088-101.
133. Suy A, Martinez E, Coll O, Lonca M, Palacio M, de Lazzari E, et al. Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. AIDS. 2006;20(1):59-66.
134. Maiques V, Garcia-Tejedor A, Diago V, Molina JM, Borras D, Perales-Puchalt A, et al. Perioperative cesarean delivery morbidity among HIV-infected women under highly active antiretroviral treatment: a case-control study. Eur J Obstet Gynecol Reprod Biol. 2010;153(1):27-31.

135. Wimalasundera RC, Larbalestier N, Smith JH, de Ruiter A, Mc GTSA, Hughes AD, et al. Pre-eclampsia, antiretroviral therapy, and immune reconstitution. Lancet. 2002;360(9340):1152-4.
136. Grubert TA, Reindell D, Kastner R, Lutz-Friedrich R, Belohradsky BH, Dathe O. Complications after caesarean section in HIV-1-infected women not taking antiretroviral treatment. Lancet. 1999;354(9190):1612-3.
137. Boer K, Nellen JF, Patel D, Timmermans S, Tempelman C, Wibaut M, et al. The AmRo study: pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. BJOG. 2007;114(2):148-55.
138. Haeri S, Shauer M, Dale M, Leslie J, Baker AM, Saddlemire S, et al. Obstetric and newborn infant outcomes in human immunodeficiency virus-infected women who receive highly active antiretroviral therapy. Am J Obstet Gynecol. 2009;201(3):315 e1-5.
139. Louis J, Buhari MA, Allen D, Gonik B, Jones TB. Postpartum morbidity associated with advanced HIV disease. Infect Dis Obstet Gynecol. 2006;2006:79512.
140. Cavasin H, Dola T, Uribe O, Biswas M, Do M, Bhuiyan A, et al. Postoperative infectious morbidities of cesarean delivery in human immunodeficiency virus-infected women. Infect Dis Obstet Gynecol. 2009;2009:827405.
141. Rodriguez EJ, Spann C, Jamieson D, Lindsay M. Postoperative morbidity associated with cesarean delivery among human immunodeficiency virus-seropositive women. Am J Obstet Gynecol. 2001;184(6):1108-11.
142. Roman-Poueriet J, Fernandez AD, Beck-Sague CM, Szabo RG, Mercedes F, Duke W, et al. HIV infection and prevention of mother-tochild transmission in childbearing women: La romana, Dominican republic, 2002-2006. Revista Panamericana de Salud Publica/Pan American Journal of Public Health. 2009;26(4):315-23.
143. Peret FJ, Melo VH, de Paula LB, de Andrade BA, Pinto JA. Puerperal morbidity in HIV-infected and non-infected women. Revista Brasileira de Ginecologia e Obstetricia. 2007;29(5):260-6.
144. Braddick MR, Kreiss JK, Embree JB, Datta P, Ndinya-Achola JO, Pamba H, et al. Impact of maternal HIV infection on obstetrical and early neonatal outcome. AIDS. 1990;4(10):1001-5.
145. van Eijk AM, Ayisi JG, Slutsker L, Ter Kuile FO, Rosen DH, Otieno JA, et al. Effect of haematinic supplementation and malaria prevention on maternal anaemia and malaria in western Kenya. Trop Med Int Health. 2007;12(3):342-52.
146. Waweru J, Mugenda O, Kuria E. Anemia in the context of pregnancy and HIV/AIDS: a case of Pumwani Maternity Hospital in Nairobi, Kenya. African Journal of Food, Agriculture, Nutrition and Development. 2009;9(2):748-63.
147. Chamiso D. Pregnancy outcome in HIV-1 positive women in Gandhi Memorial Hospital Addis Ababa, Ethiopia. East Afr Med J. 1996;73(12):805-9.
148. Wandabwa J, Doyle P, Todd J, Kiondo P, Wandabwa MA, Aziga F. Risk factors for ruptured uterus in Mulago hospital Kampala, Uganda. East Afr Med J. 2008;85(2):56-63.
149. Okong P, Biryahwaho B, Bergstrom S. Intrauterine infection after delivery: a marker of HIV-1 seropositivity among puerperal women in Uganda? Int J STD AIDS. 2004;15(10):669-72.
150. Olagbuji BN, Ezeanochie MC, Ande AB, Oboro VO. Obstetric and perinatal outcome in HIV positive women receiving HAART in urban Nigeria. Archives of Gynecology and Obstetrics. 2009;281(6).
151. Onah HE, Obi SN, Agbata TA, Oguanuo TC. Pregnancy outcome in HIV-positive women in Enugu, Nigeria. J Obstet Gynaecol. 2007;27(3):271-4.
152. Chama CM, Morrupa JY. The safety of elective caesarean section for the prevention of mother-to-child transmission of HIV-1. J Obstet Gynaecol. 2008;28(2):194-7.

153. Zvandasara P, Saungweme G, Mlambo JT, Moyo J. Post Caesarean section infective morbidity in HIV-positive women at a tertiary training hospital in Zimbabwe. Cent Afr J Med. 2007;53(9-12):43-7.
154. Moodliar S, Moodley J, Esterhuizen TM. Complications associated with caesarean delivery in a setting with high HIV prevalence rates. Eur J Obstet Gynecol Reprod Biol. 2007;131(2):138-45.
155. Urbani G, de Vries MM, Cronje HS, Niemand I, Bam RH, Beyer E. Complications associated with cesarean section in HIV-infected patients. Int J Gynaecol Obstet. 2001;74(1):9-15.
156. Singh YA, Usham R, Devi SR, Singh LR, Sangeeta N, Sushila L. Foeto-maternal outcome in HIV infected women and measures to prevent parent-to-child transmission of HIV. JMS Journal of Medical Society. 2009;23(3):116-20.
157. Chanrachakul B, Herabutya Y, Panburana P. Active management of labor: is it suitable for a developing country? Int J Gynaecol Obstet. 2001;72(3):229-34.
158. Panburana P, Phaupradit W, Tantisirin O, Sriintravanit N, Buamuenvai J. Maternal complications after Caesarean section in HIV infected pregnant women. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2003;43(2):160-3.
159. Fiore S, Newell ML, Thorne C. Higher rates of post-partum complications in HIV-infected than in uninfected women irrespective of mode of delivery. AIDS. 2004;18(6):933-8.
160. Aboud S, Msamanga G, Read JS, Wang L, Mfalila C, Sharma U, et al. Effect of prenatal and perinatal antibiotics on maternal health in Malawi, Tanzania, and Zambia. International Journal of Gynecology & Obstetrics. 2009;107(3):202-7.
161. van Dillen J, Zwart J, Schutte J, van Roosmalen J. Maternal sepsis: epidemiology, etiology and outcome. Current Opinion in Infectious Diseases. 2010;23(3):249-54 10.1097/QCO.0b013e328339257c.
162. Wasserheit JN. Epidemiological synergy. Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. Sexually transmitted diseases. 1992;19(2):61-77.
163. Clottey C, Dallabetta G. Sexually transmitted diseases and human immunodeficiency virus. Epidemiologic synergy? Infectious disease clinics of North America. 1993;7(4):753-70.
164. NCCMED. Saving Mothers 2008-2010: Fifth Report on Confidential Enquiries into Maternal Deaths in South Africa. 2012.
165. Sloand EM, Klein HG, Banks SM, Vareldzis B, Merritt S, Pierce P. Epidemiology of thrombocytopenia in HIV inlection. European Journal of Haematology. 1992;48(3):168-72.
166. Rossi G, Gorla R, Stellini R, Franceschini F, Bettinzioli M, Cadeo G, et al. Prevalence, clinical, and laboratory features of thrombocytopenia among HIV-infected individuals. AIDS Res Hum Retroviruses. 1990;6(2):261-9.
167. Scaradavou A. HIV-related thrombocytopenia. Blood Reviews. 2002;16(1):73-6.
168. The Internation Perinatal HIV Group. The Mode of Delivery and the Risk of Vertical Transmission of Human Immunodeficiency Virus Type 1 — A Meta-Analysis of 15 Prospective Cohort Studies. New England Journal of Medicine. 1999;340(13):977-87.
169. National Institute for Clinical Excellence. Clinical Guideline 13: Caesarean section. London: National Institute for Clinical Excellence; 2004.
170. National Institute for Health and Clinical Excellence. Caesarean Section. National Institute for Health and Clinical Excellence; 2011.
171. Zaba B, Calvert C, Marston M, Isingo R, Nakiyingi-Miiro J, Lutalo T, et al. Effect of HIV infection on pregnancy-related mortality in sub-Saharan Africa: secondary analyses of pooled community-based data from the network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA). The Lancet. 2013;381(9879):1763-71.

172. Sebitloane HM, Moodley J, Esterhuizen TM. Prophylactic antibiotics for the prevention of postpartum infectious morbidity in women infected with human immunodeficiency virus: a randomized controlled trial. American Journal of Obstetrics and Gynecology. 2008;198(2):189.e1-.e6.
173. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. World Health Organization; 2010.
174. World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infections in infants: recommendations for a public health approach, 2010 version. Geneva: 2010.
175. UNAIDS. Countdown to zero: Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. Geneva: UNAIDS; 2011.
176. Coutsoudis A, Goga A, Desmond C, Barron P, Black V, Coovadia H. Is Option B+ the best choice? The Lancet.381(9863):269-71.
177. Higgins JR, de Swiet M. Blood-pressure measurement and classification in pregnancy. The Lancet. 2001;357(9250):131-5.
178. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. The Lancet Global Health. 2014;2(6):e323-e33.
179. Onakewhor JU, Olagbuji BN, Ande AB, Ezeanochie MC, Olokor OE, Okonofua FE. HIV-AIDS related maternal mortality in Benin City, Nigeria. Ghana Med J. 2011;45(2):54-9.
180. Mayanja BN, Shafer LA, Van der Paal L, Kyakuwa N, Ndembi N, Hughes P, et al. Effect of pregnancy on immunological and virological outcomes of women on ART: A prospective cohort study in rural Uganda, 2004-2009. Tropical Medicine and International Health. 2012;17(3):343-52.
181. The World Bank Group. Countries and Economies 2014 [cited 2014 24/01/2014]. Available from: http://data.worldbank.org/country.
182. Alliegro MB, Dorrucci M, Phillips AN, Pezzotti P, Boros S, Zaccarelli M, et al. Incidence and consequences of pregnancy in women with known duration of HIV infection. Archives of Internal Medicine. 1997;157(22):2585-90.
183. Bessinger R, Clark R, Kissinger P, Rice J, Coughlin S. Pregnancy is not associated with the progression of HIV disease in women attending an HIV outpatient program. Am J Epidemiol. 1998;147(5):434-40.
184. Deschamps MM, Pape JW, Desvarieux M, Williams-Russo P, Madhavan S, Ho JL, et al. A prospective study of HIV-seropositive asymptomatic women of childbearing age in a developing country. J Acquir Immune Defic Syndr. 1993;6(5):446-51.
185. Allen S, Stephenson R, Weiss H, Karita E, Priddy F, Fuller L, et al. Pregnancy, hormonal contraceptive use, and HIV-related death in Rwanda. J Womens Health (Larchmt). 2007;16(7):1017-27.
186. Kumar RM, Uduman SA, Khurrana AK. Impact of pregnancy on maternal AIDS. J Reprod Med. 1997;42(7):429-34.
187. Berrebi A, Kobuch WE, Puel J, Tricoire J, Herne P, Grandjean H, et al. Influence of pregnancy on human immunodeficiency virus disease. Eur J Obstet Gynecol Reprod Biol. 1990;37(3):211-7.
188. Hocke C, Morlat P, Chene G, Dequae L, Dabis F. Prospective cohort study of the effect of pregnancy on the progression of human immunodeficiency virus infection. The Groupe d'Epidemiologie Clinique Du SIDA en Aquitaine. Obstet Gynecol. 1995;86(6):886-91.
189. Weisser M, Rudin C, Battegay M, Pfluger D, Kully C, Egger M. Does pregnancy influence the course of HIV infection? Evidence from two large Swiss cohort studies. J Acquir Immune Defic Syndr Hum Retrovirol. 1998;17(5):404-10.
190. Matthews LT, Kaida A, Kanters S, Byakwagamd H, Mocello AR, Muzoora C, et al. HIV-infected women on antiretroviral treatment have increased mortality during pregnant and postpartum periods. Aids. 2013;27(SUIPPL.1):S105-S12.

191. Westreich D, Maskew M, Evans D, Firnhaber C, Majuba P, Sanne I. Incident Pregnancy and Time to Death or AIDS among HIV-Positive Women Receiving Antiretroviral Therapy. PLoS ONE. 2013;8(3).
192. Buskin SE, Diamond C, Hopkins SG. HIV-infected pregnant women and progression of HIV disease. Arch Intern Med. 1998;158(11):1277-8.
193. Saada M, Le Chenadec J, Berrebi A, Bongain A, Delfraissy JF, Mayaux MJ, et al. Pregnancy and progression to AIDS: Results of the French prospective cohorts. Aids. 2000;14(15):2355-60.
194. Khlat M, Ronsmans C. Deaths Attributable to Childbearing in Matlab, Bangladesh: Indirect Causes of Maternal Mortality Questioned. American Journal of Epidemiology. 2000;151(3):300-6.
195. Carter RJ, Dugan K, El-Sadr WM, Myer L, Otieno J, Pungpapong N, et al. CD4+ cell count testing more effective than HIV disease clinical staging in identifying pregnant and postpartum women eligible for antiretroviral therapy in resource-limited settings. J Acquir Immune Defic Syndr. 2010;55(3):404-10.
196. Ekouevi DK, Inwoley A, Tonwe-Gold B, Danel C, Becquet R, Viho I, et al. Variation of CD4 count and percentage during pregnancy and after delivery: implications for HAART initiation in resource-limited settings. AIDS Res Hum Retroviruses. 2007;23(12):1469-74.
197. Atmar RL, Englund JA, Hammill H. Complications of Measles during Pregnancy. Clinical Infectious Diseases. 1992;14(1):217-26.
198. Haake DA, Zakowski PC, Haake DL, Bryson YJ. Early treatment with acyclovir for varicella pneumonia in otherwise healthy adults: retrospective controlled study and review. Rev Infect Dis. 1990;12(5):788-98.
199. Louie JK, Acosta M, Jamieson DJ, Honein MA. Severe 2009 H1N1 Influenza in Pregnant and Postpartum Women in California. New England Journal of Medicine. 2010;362(1):27-35.
200. Mor G, Cardenas I. REVIEW ARTICLE: The Immune System in Pregnancy: A Unique Complexity. American Journal of Reproductive Immunology. 2010;63(6):425-33.
201. Rowe JH, Ertelt JM, Xin L, Way SS. Pregnancy imprints regulatory memory that sustains anergy to fetal antigen. Nature. 2012;490(7418):102-6.
202. Okoko BJ, Enwere G, Ota MOC. The epidemiology and consequences of maternal malaria: a review of immunological basis. Acta Tropica. 2003;87(2):193-205.
203. Nduati R, Richardson BA, John G, Mbori-Ngacha D, Mwatha A, Ndinya-Achola J, et al. Effect of breastfeeding on mortality among HIV-1 infected women: a randomised trial. The Lancet. 2001;357(9269):1651-5.
204. Ledergerber B, von Overbeck J, Egger M, Luthy R. The Swiss HIV Cohort Study: rationale, organization and selected baseline characteristics. Soz Praventivmed. 1994;39(6):387-94.
205. Garenne M, Kahn K, Collinson M, Gómez-Olivé X, Tollman S. Protective Effect of Pregnancy in Rural South Africa: Questioning the Concept of “Indirect Cause” of Maternal Death. PLoS ONE. 2013;8(5):e64414.
206. Westreich D, Kipp A. Pregnancy and HIV disease progression: methodological concerns. J Infect Dis. 2008;197(7):1074-5, author reply 6-7.
207. Porter K, Zaba B. The empirical evidence for the impact of HIV on adult mortality in the developing world: data from serological studies. AIDS. 2004;18(Suppl 2):S9-S17.
208. Zaba B, Marston M, Crampin AC, Isingo R, Biraro S, Bärnighausen T, et al. Age-specific mortality patterns in HIV-infected individuals: a comparative analysis of African community study data. AIDS. 2007;21:S87-S96
209. Ahmed Y, Mwaba P, Chintu C, Grange JM, Ustianowski A, Zumla A. A study of maternal mortality at the University Teaching Hospital, Lusaka, Zambia: the emergence of tuberculosis as a major non-obstetric cause of maternal death. The International Journal of Tuberculosis and Lung Disease. 1999;3(8):675-80.

210. Chweneyagae D, Delis-Jarrosay N, Farina Z, Fawcus S, Godi NP, Khaole N, et al. The impact of HIV infection on maternal deaths in South Africa. S Afr J OG 2012;18(3):70-6.
211. Maher D, Biraro S, Hosegood V, Isingo R, Lutalo T, Mushati P, et al. Translating global health research aims into action: the example of the ALPHA network*. Tropical Medicine & International Health. 2010;15(3):321-8.
212. Jahn A, Branson K, Crampin AC, Fine PEM, Glynn JR, McGrath N, et al. Evaluation of a village-informant driven demographic surveillance system in Karonga, Northern Malawi. Demographic Research. 2007;16(8):219-48.
213. Welz T, Herbst K. Anonymous HIV Testing With Participant-Controlled Access to Results Using Handheld Computers: A New Model of HIV Testing Used in a Household Survey in Rural South Africa. Sexually Transmitted Diseases. 2008;35(4):372-6
214. Boerma JT, Urassa M, Senkoro K, Klokke A, Ng,weshemi JZL. Spread of HIV infection in a rural area of Tanzania. AIDS. 1999;13(10):1233-40.
215. Gregson S, Mason PR, Garnett GP, Zhuwau T, Nyamukapa CA, Anderson RM, et al. A rural HIV epidemic in Zimbabwe? Findings from a population-based survey. International Journal of STD & AIDS. 2001;12(3):189-96.
216. Kengeya-Kayondo J, Kamali A, Nunn A, Ruberantwari A, Wagner H, Mulder D. Incidence of HIV-1 Infection in Adults and Socio-Demographic Characteristics of Seroconverters in a Rural Population in Uganda: 1990–1994. International Journal of Epidemiology. 1996;25(5):1077-82.
217. Crampin AC, Glynn JR, Ngwira BM, Mwaungulu FD, Pönnighaus JM, Warndorff DK, et al. Trends and measurement of HIV prevalence in northern Malawi. AIDS. 2003;17(12):1817-25.
218. Welz T, Hosegood V, Jaffar S, Bätzing-Feigenbaum J, Herbst K, Newell M-L. Continued very high prevalence of HIV infection in rural KwaZulu-Natal, South Africa: a population-based longitudinal study. AIDS. 2007;21(11):1467-72
219. Kamali A, Carpenter LM, Whitworth JAG, Pool R, Ruberantwari A, Ojwiya A. Seven-year trends in HIV-1 infection rates, and changes in sexual behaviour, among adults in rural Uganda. AIDS. 2000;14(4):427-34.
220. Konde-Lule JK, Wawer MJ, Sewankambo NK, Serwadda D, Kelly R, Li C, et al. Adolescents, sexual behavior and HIV-1 in rural Rakai district, Uganda. AIDS. 1997;11(6):791-9.
221. Mwaluko G, Urassa M, Isingo R, Zaba B, Boerma JT. Trends in HIV and sexual behaviour in a longitudinal study in a rural population in Tanzania, 1994-2000. AIDS. 2003;17(18):2645-51.
222. Lopman B, Nyamukapa C, Mushati P, Mupambireyi Z, Mason P, Garnett GP, et al. HIV incidence in 3 years of follow-up of a Zimbabwe cohort—1998–2000 to 2001–03: contributions of proximate and underlying determinants to transmission. International Journal of Epidemiology. 2008;37(1):88-105.
223. Setel PW, Rao C, Hemed Y, Whiting DR, Yang G, Chandramohan D, et al. Core Verbal Autopsy Procedures with Comparative Validation Results from Two Countries. PLoS Med. 2006;3(8):e268.
224. Baiden F, Bawah A, Biai S, Binka F, Boerma T, Byass P, et al. Setting international standards for verbal autopsy. Bulletin of the World Health Organization. 2007;85:570-1.
225. Lewis JJ, Ronsmans C, Ezeh A, Gregson S. The population impact of HIV on fertility in sub-Saharan Africa. AIDS. 2004;18:S35-S43.
226. UNAIDS. Unpublished estimates from the "Global Report: UNAIDS Report on the global AIDS epidemic". Geneva: UNAIDS; 2012.
227. NCCMED. Saving Mothers 2005-2007: Fourth Report on Confidential Enquiries into Maternal Deaths in South Africa. 2008.
228. Nyirenda M, Zaba B, Bärnighausen T, Hosegood V, Newell M-L. Adjusting HIV Prevalence for Survey Non-Response Using Mortality Rates: An Application of the

Method Using Surveillance Data from Rural South Africa. PLoS ONE. 2010;5(8):e12370.
229. Menéndez C, Romagosa C, Ismail MR, Carrilho C, Saute F, Osman N, et al. An Autopsy Study of Maternal Mortality in Mozambique: The Contribution of Infectious Diseases. PLoS Med. 2008;5(2):e44.
230. Lopman BA, Barnabas RV, Boerma JT, Chawira G, Gaitskell K, Harrop T, et al. Creating and Validating an Algorithm to Measure AIDS Mortality in the Adult Population using Verbal Autopsy. PLoS Med. 2006;3(8):e312.
231. InterVA-4 User Guide. Available from: http://www.globalhealthaction.net/index.php/gha/article/view/19281. 2012.
232. Byass P, Fottrell E, Dao LH, Berhane Y, Corrah T, Kahn K, et al. Refining a probabilistic model for interpreting verbal autopsy data. Scand J Public Health. 2006;34(1):26-31.
233. Byass P, Huong DL, Minh HV. A probabilistic approach to interpreting verbal autopsies: methodology and preliminary validation in Vietnam. Scand J Public Health Suppl. 2003;62:32-7.
234. Kanjala C, Michael D, Todd J, Slaymaker E, Calvert C, Isingo R, et al. Using HIV-attributable mortality to assess the impact of antiretroviral therapy on adult mortality in rural Tanzania. Glob Health Action. 2014;7:21865.
235. Byass P, Kahn K, Fottrell E, Mee P, Collinson MA, Tollman SM. Using verbal autopsy to track epidemic dynamics: the case of HIV-related mortality in South Africa. Popul Health Metr. 2011;9:46.
236. Bell JS, Ouedraogo M, Ganaba R, Sombie I, Byass P, Baggaley RF, et al. The epidemiology of pregnancy outcomes in rural Burkina Faso. Trop Med Int Health. 2008;13 Suppl 1:31-43.
237. Cummings P. Methods for estimating adjusted risk ratios. Stata Journal. 2009;9(2):175-96.
238. Li Z, McCormick T, Clark S. Package `InterVA-4". Available from http://cran.stat.ucla.edu/web/packages/InterVA4/InterVA4.pdf. [cited 31 July 2014].
239. Oti SO, Wamukoya M, Mahy M, Kyobutungi C. InterVA versus Spectrum: how comparable are they in estimating AIDS mortality patterns in Nairobi's informal settlements? Glob Health Action. 2013;6:21638.
240. Tensou B, Araya T, Telake DS, Byass P, Berhane Y, Kebebew T, et al. Evaluating the InterVA model for determining AIDS mortality from verbal autopsies in the adult population of Addis Ababa. Trop Med Int Health. 2010;15(5):547-53.
241. Grinsztejn B, Luz PM, Pacheco AG, Santos DVG, Velasque L, Moreira RI, et al. Changing Mortality Profile among HIV-Infected Patients in Rio de Janeiro, Brazil: Shifting from AIDS to Non-AIDS Related Conditions in the HAART Era. PLoS ONE. 2013;8(4):e59768.
242. Grollman C. Assigning HIV/AIDS as a cause of adult death using verbal autopsy: performance of three methods and their effects on estimates of HIV/AIDS-related mortality London School of Hygiene and Tropical Medicine; 2014.
243. Smaill FM, Gyte GM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database Syst Rev. 2010(1):Cd007482.
244. Bamfo JEAK. Managing the risks of sepsis in pregnancy. Best Practice & Research Clinical Obstetrics & Gynaecology. 2013;27(4):583-95.
245. Souza JP, Gulmezoglu A, Lumbiganon P, Laopaiboon M, Carroli G, Fawole B, et al. Caesarean section without medical indications is associated with an increased risk of adverse short-term maternal outcomes: the 2004-2008 WHO Global Survey on Maternal and Perinatal Health. BMC Med. 2010;8:71.
246. Suthar AB, Hoos D, Beqiri A, Lorenz-Dehne K, McClure C, Duncombe C. Integrating antiretroviral therapy into antenatal care and maternal and child health settings: a systematic review and meta-analysis. Bull World Health Organ. 2013;91(1):46-56.

247. Lindegren ML, Kennedy CE, Bain-Brickley D, Azman H, Creanga AA, Butler LM, et al. Integration of HIV/AIDS services with maternal, neonatal and child health, nutrition, and family planning services. Cochrane Database Syst Rev. 2012;9:Cd010119.
248. Gorman SE. A new approach to maternal mortality: the role of HIV in pregnancy. Int J Womens Health. 2013;5:271-4.
249. World Health Organization. Consolidated Guidelines on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Geneva: World Health Organization; 2013.
250. Centers for Disease Control and Prevention. Impact of an Innovative Approach to Prevent Mother-to-Child-Transmission of HIV - Malawi, July 2011-September 2012. Morbidity and Mortality Weekly Report (MMWR). 2013;62(8):148-51.
251. Shaffer N, Abrams EJ, Becquet R. Option B+ for prevention of mother-to-child transmission of HIV in resource-constrained settings: great promise but some early caution. Aids. 2014;28(4):599-601.
252. Tenthani L, Haas AD, Tweya H, Jahn A, van Oosterhout JJ, Chimbwandira F, et al. Retention in care under universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women ('Option B+') in Malawi. Aids. 2014;28(4):589-98.
253. Price AJ, Kayange M, Zaba B, Chimbwandira FM, Jahn A, Chirwa Z, et al. Uptake of prevention of mother-to-child-transmission using Option B+ in northern rural Malawi: a retrospective cohort study. Sex Transm Infect. 2014;90(4):309-14.
254. Colvin CJ, Konopka S, Chalker JC, Jonas E, Albertini J, Amzel A, et al. A Systematic Review of Health System Barriers and Enablers for Antiretroviral Therapy (ART) for HIV-Infected Pregnant and Postpartum Women. PLoS ONE. 2014;9(10):e108150.
255. Sturt AS, Dokubo EK, Sint TT. Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women. Cochrane Database Syst Rev. 2010(3):Cd008440.
256. Grollman C. Assigning HIV/AIDS as a cause of adult death using verbal autopsy: performance of three methods and their effects on estimates of HIV/AIDS-related mortality: London School of Hygiene and Tropical Medicine; 2014.
257. Bassat Q, Ordi J, Vila J, Ismail MR, Carrilho C, Lacerda M, et al. Development of a post-mortem procedure to reduce the uncertainty regarding causes of death in developing countries. The Lancet Global Health. 2013;1(3):e125-e6.

Appendix A Systematic Review Protocol

REVIEW 1

Objective

To establish whether HIV increases mortality risk during pregnancy, childbirth and in the one year postnatal period

Criteria for considering studies in this review

Types of studies

Include: Cohort, RCTs, Case-control, census

Exclude: case reports, comment, practice guidelines, editorial, consensus development conference, guideline, legal cases, legislation, newspaper article, patient education handout, retracted publication

Types of participants

Exposed Group: HIV positive pregnant women
Comparison Group: HIV negative pregnant women

Type of outcome measure

Mortality (according to either a pregnancy-related or maternal definition) during pregnancy, delivery and/or up to one year postpartum.

Search methods

Methods of the review

We will search the following databases: PUBMED, EMBASE, Popline and African Index Medicus. Reference lists of relevant articles will also be searched.

Selection of the studies

Inclusion criteria

1. Countries: All
2. Date of Publication: All
3. Language: All
4. Facility or community based studies: All

Exclusion criteria

1. Sample size<30 in either study group
2. Case reports
3. Data duplicated in other studies
4. Conference abstracts
5. Studies where HIV status was assessed according to clinical criteria rather than using HIV testing

Data extraction and management

All references will be imported into Endnote. References will initially be screened using a title and abstracts approach. A 20% sample will be selected systematically (50 abstracts per 500 abstracts, organised in alphabetical order according to the authors name) and screened by a second researcher to cross check identification of articles by the main screener. Then, references thought to be of possible use will be obtained, and read in greater depth. Articles that fulfil the inclusion criteria will be extracted. For non-English language papers we will seek someone to translate the article.

A database will be set up in Excel. Data extracted will include the following:

1. Study reference
2. Dates of Study
3. Study design
4. Study setting
    a. Country
    b. Region
    c. Rural or urban
    d. Facility or population based
5. Study population
    a. Inclusion/exclusion criteria
    b. Method of selecting HIV infected women
    c. Method of selecting HIV uninfected women
    d. Was there any evidence for any differences between the two study groups in socio-demographic characteristics
6. Whether women with HIV were given ART
7. The prevalence of HIV in the study population
8. Length of follow up
9. Sample size
    a. Size of exposed group
    b. Size of comparison group
10. Outcomes
    a. Method of identifying mortality (e.g. hospital notes, prospective follow up, census data)
    b. Number of women who died in exposed/ unexposed group
    c. Total person-years of follow up (where necessary)
11. Indicators of quality of study
    a. Loss to follow up
    b. Refusal rate
    c. Any adjustment for confounders

Quality Assessment

Studies will be classified as of inadequate quality according to the following criteria:

Quality Criterion	Criteria for inadequate assessment
Loss to follow up	• >20% of women lost to follow up (in either study group) • >20% of deaths with unknown HIV status • No information provided

Adjustment for confounders	• No adjustment or no attempt to match the HIV+ and HIV- women on potential confounders
Pregnancy-related death definition	• Definition did not state length of postpartum period of follow up
Ascertainment of pregnancy-related death	• High likelihood of missing maternal deaths (e.g. hospital record review)
Selection of comparison groups	• HIV- women are not representative of the population from which the HIV+ women were selected

Data Analysis

1. We will use meta-analyses to determine the increased risk of mortality associated with HIV during pregnancy and in the postpartum period
2. We will carry out stratified meta-analyses by region, period of follow up and by art availability

REVIEW 2

Objective

To establish whether HIV increases the risk of direct obstetric complications

Criteria for considering studies in this review

Types of studies

Include: Cohort, RCTs, Case-control, census

Exclude: case reports, comment, practice guidelines, editorial, consensus development conference, guideline, legal cases, legislation, newspaper article, patient education handout, retracted publication

Types of participants

Exposed Group: HIV positive pregnant women
Comparison Group: HIV negative pregnant women

Type of outcome measure

Obstetric haemorrhage
- Antepartum haemorrhage
- Placental abruption
- Placenta praevia
- Postpartum haemorrhage
- Retained placenta

Hypertensive disorders of pregnancy
- Pregnancy-induced hypertension
- Pre-eclampsia
- Eclampsia

Dystocia
- Dystocia
- Prolonged labour
- Obstructed labour
- Uterine rupture
- Abnormal presentation

Intrauterine infections
- Sepsis
- Endometritis
- Wound infection (for caesarean only studies)

Search methods

We will search the following databases: PUBMED, EMBASE, Popline and African Index Medicus. Reference lists of relevant articles will also be searched.

Selection of the studies

Inclusion criteria

1. Countries: All
2. Date of Publication: All
3. Language: All
4. Facility or community based studies: All

Exclusion criteria

1. Sample size<30 in either study group
2. Case reports
3. Data duplicated in other studies
4. Conference abstracts

Data extraction and management

All references will be imported into Endnote. References will initially be screened using a title and abstracts approach. A 20% sample will be selected systematically (50 abstracts per 500 abstracts, organised in alphabetical order according to the authors name) and screened by a second researcher to cross check identification of articles by the main screener. Then, references thought to be of possible use will be obtained, and read in greater depth. Articles that fulfil the inclusion criteria will be extracted. For non-English language papers we will seek someone to translate the article.

A database will be set up in Excel. Data extracted will include the following:

1. Study reference
2. Dates of Study
3. Study design
4. Study setting
    a. Country
    b. Region
    c. Rural or urban
    d. Facility or population based
5. Study population
    a. Inclusion/exclusion criteria
    b. Method of selecting HIV infected women
    c. Method of selecting HIV uninfected women
    d. Was there any evidence for any differences between the two study groups in socio-demographic characteristics
6. Whether women with HIV were given ART
7. The prevalence of HIV in the study population
8. Mode and management of delivery in each study group
9. Length of follow up
10. Sample size
    a. Size of exposed group
    b. Size of comparison group
11. Outcomes
    a. Method of identifying obstetric complication (e.g. hospital notes, prospective follow up, census data)
    b. Definition of obstetric complication
    c. Number of women who with obstetric complication in exposed/ unexposed group

d. Total person-years of follow up (where necessary)

12. Indicators of quality of study
    a. Loss to follow up
    b. Refusal rate
    c. Any adjustment for confounders

Quality Assessment

Studies will be classified as of high risk of bias according to the following criteria:

Quality Criterion	Criteria for high risk
Loss to follow up	Depending on study design: • >20% of women lost to follow up (in either study group) • >20% refusal rate • >20% of medical not available or missing key information
Adjustment for confounders	• No adjustment or no attempt to match the HIV+ and HIV- women on potential confounders
Definition of outcome	• Did not provide a definition for outcome(s)
Ascertainment of outcome	• High likelihood of missing maternal deaths (e.g. hospital record review)

The study will be classified as at an unclear risk of bias if information is not provided to judge the studies as high or low risk of bias according to the criteria above.

Data Analysis

1. We will use meta-analyses to determine the association between HIV and each obstetric complications – these analyses will be stratified by mode of delivery (studies which included vaginal deliveries vs. studies which only included caesarean deliveries)

REVIEW 3

Objective

To establish whether pregnancy accelerates the progression of HIV

Criteria for considering studies in this review

Types of studies

Include: Cohort, RCTs, Case-control

Exclude: case reports, comment, practice guidelines, editorial, consensus development conference, guideline, legal cases, legislation, newspaper article, patient education handout, retracted publication

Types of participants

Exposed Group: HIV positive pregnant women
Comparison Group: HIV positive non-pregnant women

Type of outcome measure

- All-cause Mortality
- AIDS related Mortality
- Occurrence of an AIDS-defining illness
- Drop of CD4 below a threshold level
- Occurrence of a condition indicative of symptomatic HIV (e.g. oral thrush, herpes zoster, oral hairy leukoplakia)

Search methods

We will search the following databases: PUBMED, EMBASE, Popline and African Index Medicus. Reference lists of relevant articles will also be searched.

Selection of the studies

Inclusion criteria

1. Countries: All
2. Date of Publication: All
3. Language: All
4. Facility or community based studies: All

Exclusion criteria

1. Case reports
2. Data duplicated in other studies
3. Conference abstracts

Data extraction and management

All references will be imported into Endnote. References will initially be screened using a title and abstracts approach. A 20% sample will be selected systematically (50 abstracts per 500 abstracts, organised in alphabetical order according to the authors

name) and screened by a second researcher to cross check identification of articles by the main screener. Then, references thought to be of possible use will be obtained, and read in greater depth. Articles that fulfil the inclusion criteria will be extracted. For non-English language papers we will seek someone to translate the article.

A database will be set up in Excel. Data extracted will include the following:

1. Study reference
2. Dates of Study
3. Study design
4. Study setting
    a. Country
    b. Region
    c. Rural or urban
    d. Facility or population based
5. Study population
    a. Inclusion/exclusion criteria
    b. Definition of pregnant group
    c. Definition of non-pregnant group
6. Whether women were given ART, and whether this varied by pregnancy status
7. The prevalence of HIV in the study population
8. Length of follow up by pregnancy status
9. Sample size
    a. Size of exposed group (person-years where reported)
    b. Size of comparison group (person-years where reported)
10. Outcomes
    a. Method of identifying outcome
    b. Definition of HIV disease progression
    c. Number of women who experienced HIV disease progression in exposed/ unexposed group
11. Effect estimates
    a. Type of effect estimate (risk ratio/rate ratio/odds ratio
    b. Crude and/or adjusted effect estimate as reported in paper
    c. Confounders

Quality Assessment

Studies will be classified as of high risk of bias according to the following criteria:

Quality Criterion	Criteria for high risk
Identifying pregnancy	Methods which are likely to miss pregnancies (e.g. clinical review or self-report) are used
Defining non pregnant group	May include woman who were pregnant between HIV seroconversion and study entry in the non-pregnant group
Ascertainment of outcome	Pregnant and non-pregnant woman are not monitored at the same frequency
Length of follow up	Length of follow-up differs in the pregnant and non-pregnant women
Adjustment for healthy pregnant woman effect	Do not try to adjust for differences in HIV stage/CD4 count between pregnant and non-pregnant women
Adjustment for confounders	Do not adjust or match pregnant and non-pregnant women for any confounders

The study will be classified as at an unclear risk of bias if information is not provided to judge the studies as high or low risk of bias according to the criteria above.

Data Analysis

Random effects meta-analyses will be conducted to produce the follow summary relative risks:

1. Overall estimate
2. Stratified by:
    a. ART availability
    b. High income/ versus low income countries
    c. Population versus facility based studies
    d. Quality criteria

Amendments to protocol after data extraction began:

- Added in: methods of adjusting for HIV disease stage
- Added in: information on median time to event

Amendments to protocol after data analysis began:

- Added in: check for publication bias across each outcome

Appendix B Systematic Review Search Strategy

PUBMEB SEARCH STRATEGY

Search 1: HIV terms

HIV OR “human immunodeficiency virus” OR AIDS OR “acquired immunodeficiency syndrome” OR HIV/AIDS OR HIV[MeSH] OR “HIV Infections”[MeSH] or "acquired immunodeficiency syndrome"[MeSH]

Search 2: Maternal/pregnancy terms

matern* OR pregnan* OR childbirth OR intrapartum OR intra-partum OR postpartum OR postpartum OR puerperal OR puerperium OR parturition OR “expectant mother” OR “expectant mothers” OR “maternal health services”[MeSH] OR “delivery, obstetric”[MeSH] OR parturition[MeSH] OR pregnancy [MeSH] OR “Delivery, Obstetric”[MeSH] OR “postpartum period”[MeSH]

Search 3: Objective 1 specific terms (mortality)

mortalit* OR fatalit* OR “fatal outcome” OR death OR deaths OR death[MeSH] OR mortality[MeSH]

Search 4: Objective 2 specific terms (obstetric complications)

morbidit* OR “pregnancy complication” OR “complication of pregnancy” OR “obstetric complication” OR “obstetric labor complication” OR “obstetric labour complication” OR “adverse pregnancy outcome” OR ((postpartum OR postpartum) AND (haemorrhage OR hemorrhage)) OR ((obstetric) AND (haemorrhage OR hemorrhage)) OR hemorrhage OR “vaginal bleeding” OR ((antepartum OR ante-partum) AND (haemorrhage OR hemorrhage)) OR dystocia OR ((obstructed OR prolonged) AND (labour OR labor)) OR “retained placenta” OR “pregnancy induced hypertension” OR hellp OR eclampsia OR preeclampsia OR “pre-eclampsia” OR “gestational diabetes” OR “abruptio placent*” OR “placental abruption” OR “placenta previa” OR "placenta praevia" OR “ruptured uterus” OR sepsis OR septic OR septicemia OR septicemic OR

endometritis OR “puerperal infection” OR “near miss” OR “near-miss” OR “caesarean section” OR c-section OR “caesarian section” OR “cesarean section” OR anaemia OR anemia OR “iron deficien*” OR “obstetric labor complications”[MeSH] OR “pregnancy complications”[MeSH] OR hemorrhage[MeSH] OR “postpartum haemorrhage”[MeSH] OR “uterine inversion”[MeSH] OR “uterine hemorrhage”[MeSH] OR dystocia[MeSH] OR "placenta, retained"[MeSH] OR "hypertension, pregnancy-induced"[MeSH] OR "hellp syndrome"[MeSH Terms] OR eclampsia[MeSH] OR pre-eclampsia[MeSH] OR "diabetes, gestational"[MeSH] OR "abruptio placentae"[MeSH] OR "placenta previa"[MeSH] OR "uterine rupture"[MeSH] OR sepsis[MeSH] OR "cesarean section"[MeSH Terms] OR "anemia"[MeSH Terms]

Search 5: Objective 3 specific terms (HIV disease progression)

“CD4 lymphocyte count” OR “CD4 count” OR (HIV AND “disease progression”) OR “HIV severity” OR “aids defining” OR “AIDS-related opportunistic Infections” OR “kaposi's sarcoma” OR lymphoma OR “wasting syndrome” OR cachexia OR “pneumocystis carinii” OR tuberculosis OR tb OR “symptomatic HIV” OR “opportunistic infection” OR “opportunistic infections” OR “CD4 lymphocyte count”[MeSH] OR “AIDS-related opportunistic Infections”[MeSH] OR "lymphoma"[MeSH] OR "cachexia"[MeSH] OR "tuberculosis"[MeSH]

Search 6*:* Objective 4 specific terms (HIV incidence)

seroconversion OR incidence OR "incidence"[MeSH] OR "HIV infections/transmission"[MeSH]

FINAL SEARCH: (#1 AND #2 AND (#3 OR #4 OR #5 OR #6))

EMBASE SEARCH STRATEGY

Search 1: HIV terms

HIV OR human immunodeficiency virus OR HIV infections OR AIDS OR acquired immunodeficiency syndrome OR HIV/AIDs OR exp human immunodeficiency virus/ OR exp human immunodeficiency virus infection/ OR exp acquired immune deficiency syndrome/

Search 2: Maternal/pregnancy terms

matern* OR mother* OR pregnan*OR childbirth OR intrapartum OR intra-partum OR postpartum OR postpartum OR puerperal OR puerperium OR parturition OR expectant mother* OR exp expectant mother/ OR exp birth/ OR exp childbirth/ OR exp pregnancy/ OR exp delivery/

Search 3: Objective 1 specific terms (mortality)

mortalit*OR maternal mortality OR fatalit* OR fatal outcome OR death* OR exp mortality/ OR exp maternal mortality/ OR exp fatality/ OR exp death/

Search 4: Objective 2 specific terms (obstetric complications)

morbidit* OR pregnancy complication OR complication of pregnancy OR obstetric complication OR obstetric labor complication OR obstetric labour complication OR adverse pregnancy outcome OR ((postpartum OR postpartum) AND (haemorrhage OR hemorrhage)) OR ((obstetric) AND (haemorrhage OR hemorrhage)) OR hemorrhage OR vaginal bleeding OR ((antepartum OR ante-partum) AND (haemorrhage OR hemorrhage)) OR dystocia OR ((obstructed OR prolonged) AND (labour OR labor)) OR retained placenta OR pregnancy induced hypertension OR hellp OR eclampsia OR preeclampsia OR pre-eclampsia OR gestational diabetes OR abruptio placent* OR placental abruption OR placenta previa OR placenta praevia OR ruptured uterus OR sepsis OR septic OR septicemia OR septicemic OR endometritis OR puerperal infection OR near miss OR near-miss OR caesarean section OR c-section OR caesarian section OR cesarean section OR anaemia OR anemia OR iron deficien* OR exp morbidity/ OR exp maternal morbidity/ OR exp pregnancy complication/ OR exp labor

complication/ OR exp postpartum hemorrhage/ OR exp bleeding/ OR antepartum hemorrhage/ OR exp obstetric hemorrhage/ OR exp dystocia/ OR exp retained placenta/ OR exp maternal hypertension/ OR exp HELLP syndrome/ OR exp "eclampsia and preeclampsia"/ OR exp pregnancy diabetes mellitus/ OR exp placenta previa/ OR exp uterus rupture/ OR exp sepsis/ OR exp septic shock/ OR exp septicemia/ OR exp endometritis/ OR exp puerperal infection/ OR exp cesarean section/ OR exp anemia/ OR exp iron deficiency anemia/

Search 5: Objective 3 specific terms (HIV disease progression)

CD4 lymphocyte count OR CD4 count OR HIV disease progression OR HIV severity OR aids defining OR AIDS-related opportunistic Infections *OR* kaposi's sarcoma OR lymphoma OR wasting syndrome OR cachexia OR pneumocystis carinii OR tuberculosis *OR* tb *OR* symptomatic HIV OR opportunistic infection* *OR* exp CD4 lymphocyte count/ OR exp disease course/ OR exp AIDS related complex/ OR exp kaposi sarcoma/ OR exp lymphoma/ OR exp wasting syndrome/ OR exp cachexia/ OR exp pneumocystis carinii/ OR exp tuberculosis/ OR exp opportunistic infection/

Search 6*:* Objective 4 specific terms (HIV incidence)

seroconversion OR incidence OR exp seroconversion/ OR exp incidence/ OR exp disease transmission/

FINAL SEARCH: (#1 AND #2 AND (#3 OR #4 OR #5 OR #6))

POPLINE SEARCH STRATEGY

Search 1: HIV terms

(HIV/"human immunodeficiency virus" / AIDS / "acquired immunodeficiency syndrome" / "HIV Infections")

Search 2: Maternal/pregnancy terms

(matern* / pregnan* / childbirth / intrapartum / intra-partum / postpartum / postpartum / puerperal / puerperium / parturition / "expectant mother" / "expectant mothers")

Search 3: Objective 1 specific terms (mortality)

(mortalit* / fatalit* / death*)

Search 4: Objective 2 specific terms (obstetric complications)

(morbidit* / "pregnancy complication" / "obstetric complication" / "obstetric labor complication" / "obstetric labour complication" / "adverse pregnancy outcome" / "postpartum haemorrhage" / "postpartum hemorrhage" / "obstetric haemorrhage" / "obstetric hemorrhage" / hemorrhage / "vaginal bleeding" / "antepartum haemorrhage" / "antepartum hemorrhage" / dystocia / "obstructed labour" / "obstructed labor" / "prolonged labour" / "prolonged labor" / "retained placenta" / "pregnancy induced hypertension" / hellp / eclampsia / preeclampsia / "pre-eclampsia" / "gestational diabetes" / "abruptio placent*" / "placental abruption" / "placenta previa" / "placenta praevia" / "ruptured uterus" / sepsis / septic / septicemia / septicemic / endometritis / "puerperal infection" / "near miss" / "near-miss" / "caesarean section" / c-section / "caesarian section" / "cesarean section" / anaemia / anemia)

Search 5: Objective 3 specific terms (HIV disease progression)

("CD4 lymphocyte count" **/** "CD4 count" **/** "HIV disease progression" / "HIV severity" / "aids defining" **/ "**AIDS-related opportunistic Infections" **/** "kaposi's sarcoma" / lymphoma / "wasting syndrome" / cachexia / "pneumocystis carinii" / tuberculosis **/** tb / "symptomatic HIV" / "opportunistic infection*"**)**

Search 6*:* Objective 4 specific terms (HIV incidence)

(seroconversion / incidence)

FINAL SEARCH (advanced search in title/keywords and abstract)

(HIV/"human immunodeficiency virus" / AIDS / "acquired immunodeficiency syndrome" / "HIV Infections") **&** (matern* / pregnan* / childbirth / intrapartum / intra-partum / postpartum / postpartum / puerperal / puerperium / parturition / "expectant mother" / "expectant mothers") **&** ((mortalit* / fatalit* / death*) ***/*** (morbidit* / "pregnancy complication" / "obstetric complication" / "obstetric labor complication" / "obstetric labour complication" / "adverse pregnancy outcome" / "postpartum haemorrhage" / "postpartum hemorrhage" / "obstetric haemorrhage" / "obstetric hemorrhage" / hemorrhage / "vaginal bleeding" / "antepartum haemorrhage" / "antepartum hemorrhage" / dystocia / "obstructed labour" / "obstructed labor" / "prolonged labour" / "prolonged labor" / "retained placenta" / "pregnancy induced hypertension" / hellp / eclampsia / preeclampsia / "pre-eclampsia" / "gestational diabetes" / "abruptio placent*" / "placental abruption" / "placenta previa" / "placenta praevia" / "ruptured uterus" / sepsis / septic / septicemia / septicemic / endometritis / "puerperal infection" / "near miss" / "near-miss" / "caesarean section" / c-section / "caesarian section" / "cesarean section" / anaemia / anemia) ***/*** ("CD4 lymphocyte count" ***/*** "CD4 count" / "HIV disease progression" / "HIV severity" / "aids defining" / ***"***AIDS-related opportunistic Infections*"* ***/*** "kaposi's sarcoma" / lymphoma / "wasting syndrome" / cachexia / "pneumocystis carinii*"* / tuberculosis / *tb / "*symptomatic HIV" / "opportunistic infection****") /*** (seroconversion / incidence))

AFRICAN INDEX MEDICUS SEARCH STRATEGY

HIV terms:

HIV, human immunodeficiency virus, AIDS, acquired immunodeficiency syndrome

Maternal/pregnancy terms:

Maternal, Pregnancy, childbirth, intrapartum, intra-partum, postpartum, postpartum, puerperal, puerperium, parturition

Searches conducted:

1. Maternal HIV
2. Pregnancy HIV
3. Puerperium HIV
4. Maternal human immunodeficiency virus
5. Maternal AIDS
6. Pregnancy AIDS
7. Maternal acquired immunodeficiency syndrome
8. Pregnancy acquired immunodeficiency syndrome
9. Puerperium acquired immunodeficiency syndrome

Appendix C ALPHA data specifications

Specification 6.1: Essential data for each residence episode – one record per episode, include children

Variable name	Description	Coding	Notes
idno	Person ID number	site specific	Numeric IDs long integer format, unique for an individual
study_name	Name of your study field site	site specific	Character – please be consistent across data sets
sex	Male or female	1 Male 2 Female	
dob	Date of birth- best estimate	in STATA format (days since 1st Jan 1960).	If actual month and day are not known it is OK to impute, e.g. assign to middle of the month or mid-year
residence	Type of area within DSS	site-specific grouping, expect 2 to 4 categories	Aim to distinguish urban / rural, or among rural areas distinguish remote / roadside, or by dominant industry
entry_date	Date of start of residence episode	in STATA format	This date should be known quite accurately – it could be the date of a household interview or in between two recent interviews
entry_type	Type of entry	1 baseline recruitment 2 birth 3 in-migration	
exit_date	Date of end of residence episode	in STATA format	For individuals remaining resident in the study area this will be date of last household interview
exit_type	Type of exit	1 present in study site 2 death 3 out-migration 4 lost to follow-up	Code 1 refers to those alive and still resident in study area – they will be treated as censored at last interview date when known to be in study population

Specification 6.2a: HIV status: alternative (a) – summary HIV test data – one record per individual who has ever tested

Variable name	Description	Coding	Notes
idno	Person ID number	site specific	Numeric IDs long integer format, unique for an individual
study_name	Name of your study field site	site specific	Character – please be consistent across data sets
frst_neg_date	Date of first negative HIV test	in STATA format	coded not available "." for those whose first HIV test was positive
last_neg_date	Date of last negative HIV test	in STATA format	coded not available "." for those whose first HIV test was positive, may be equal to first negative date for those with only one negative test
frst_pos_date	Date of first positive HIV test	in STATA format	coded not available "." for those who have never tested positive
last_pos_date	Date of last positive HIV test	in STATA format	coded not available "." for those who have never tested positive, may be equal to first positive date for those with only one positive

			test
sero_conv_date	Estimated sero-conversion date	in STATA format	Only necessary to include this if your site estimates sero-conversion date in a way other than the mid-point between last negative and first positive HIV test

Specification 6.2b: HIV status: alternative (b) – one record for every test recorded or reported in the study

Variable name	Description	Coding	Notes
idno	Person ID number	site specific	Numeric IDs long integer format, unique for an individual
study_name	Name of your study field site	site specific	Character – please be consistent across data sets
hiv_test_date	date of HIV test	in STATA format	If test carried out in survey or study clinic date will be known exactly, if retrospectively reported by respondent may be approximated to mid-month or mid-year
hiv_test_result	HIV test result	0 negative 1 positive 2 indeterminate 3 not reported	indeterminate means test was part of study, but results were inconclusive; not reported means that participant said they had an HIV test outside of study setting but did not disclose result in interview
informed_of_result	whether or not the participant was informed of test result	0 no 1 yes	no codes typical for anonymised tests in sero-surveys; yes codes typical for VCT
location_of_test	whether test was carried out in study area and recorded as part of research record	1 part of community survey 2 study clinic or test centre 3 reported by participant, not part of study	to distinguish between routine tests in surveys, extra tests in study clinics with results recorded in study data base, and outside tests retrospectively reported by participant

Specification 7.2: Reported births, females only, one record for <u>each birth reported by all mothers</u> in DSS

Variable name	Description	Coding	Notes
idno	Person ID number	site specific	Numeric IDs long integer format, unique for an individual
study_name	Name of your study field site	site specific	Character – please be consistent across data sets
m_delivery_date	Date of reported birth	in STATA format	This may be an imputed value or actual date if reported
m_delivery_date_imp	Whether date of birth was imputed	0 no 1 yes	e.g. halfway between interviews if no information available
m_child_id	Child's unique ID if collected		
m_delivery_loc	Place of delivery	0 Home 1 Heath Centre 2 Hospital	If more codes please add to end of list
m_parity	Parity of birth		If live birth

m_stillborn	Was it a still birth?	0 no 1 yes	

Specification 7.3: Pregnancy and background characteristics, females only, one record for <u>each DSS interview</u>

Variable name	Description	Coding	Notes
idno	Person ID number	site specific	Numeric IDs long integer format, unique for an individual
study_name	Name of your study field site	site specific	Character – please be consistent across data sets
date_int	Date of interview	in STATA format	
survey_name	Which survey interview was part of	site specific	For example round1, round2, sero1, sero2
pregnant	Currently pregnant	0 no 1 yes 88 Don't know 99 Question not asked	
marital_status		0 "Never married/cohabited" 1 "Currently married mono" 2 "Currently married Poly" 3 "Currently married" 4 "Currently cohabiting" 5 "Widowed" 6 "Separated/divorced" 7 "Married but living apart" 8 "Widowed/divorced/separated" 88 Don't know 99 Question not asked	The categories listed here should enable all study centres to contribute as much detail as possible. For example if the coding used in your study enables you to know if the person is married but not whether their marriage is monogamous or polygamous you can use category 3, if your study distinguishes between monogamous and polygamous marriages you can use categories 1 and 2 respectively.
education_level	Highest education level	site specific 88 Don't know 99 Question not asked	

Specification 8.1: InterVA input file – one record for <u>each adult death</u> with VA (adults = age at death 12+ years)

Variable name	Description	Coding	Notes
idno	Person ID number	site specific	Numeric IDs long integer format, unique for an individual
study_name	Name of your study field site	site specific	Character – please be consistent across data sets
va_interview_date	Date of VA interview	in STATA format	
va_date_of_death	Reported date of death	in STATA format	
va_age_at_death	Age at death in years	12-89 as reported 90 = 90+ 99 not stated	Code as stated in VA interview – consistency checks with DSS date of birth will be performed in do-file
va_sex	Male or female	1 Male 2 Female	Code as stated in VA interview – consistency checks with DSS sex will be performed in do-file
va_final_ill	Did final illness last at least 3 weeks?	0 no, 1 yes	Stata code "." if question not asked or answer not known
va_sudden	Was death very sudden or unexpected	0 no, 1 yes	- " -
va_vis_bl	Any blurred vision	0 no, 1 yes	- " -
va_drowsy	Any drowsiness	0 no, 1 yes	- " -
va_bed_day	Was bed-bound for more than 1wk before death	0 no, 1 yes	- " -
va_coma	Was there a coma > 24hrs	0 no, 1 yes	- " -
va_collapse	Did death follow sudden collapse	0 no, 1 yes	- " -
va_season	Season of death	0 dry, 1 wet	- " -
va_injury	Any obvious recent injury	0 no, 1 yes	- " -
va_transport	Was s/he in a transport accident	0 no, 1 yes	- " -
va_drowning	Did s/he drown	0 no, 1 yes	- " -
va_fall	Had s/he fallen recently	0 no, 1 yes	- " -
va_poison	Any poisoning, bite, sting	0 no, 1 yes	- " -
va_homicide	Any suggestion of homicide	0 no, 1 yes	- " -
va_suicide	Any suggestion of suicide	0 no, 1 yes	- " -
va_smoking	Was s/he a known smoker	0 no, 1 yes	- " -
va_alcohol	Was s/he known to drink alcohol	0 no, 1 yes	- " -
va_convul	Any convulsions or fits	0 no, 1 yes	- " -
va_headache	Any headache	0 no, 1 yes	- " -
va_paralysis	Was there paralysis	0 no paralysis 1 one side 2 both sides	- " -
va_stiff_neck	Any stiff neck	0 no, 1 yes	- " -
va_or_cand	Any oral candidiasis	0 no, 1 yes	- " -
va_rigidity	Any rigidity/lockjaw	0 no, 1 yes	- " -
va_hair	Any abnormal hair colouring	0 no, 1 yes	- " -
va_ch_pain	Any chest pain	0 no, 1 yes	- " -

va_cough_long	How long did cough last	0 no cough 1 ≤ 3 weeks 2 > 3 weeks 3 had cough, duration not known	- " -
va_cough_pr	Any productive cough	0 no, 1 yes	- " -
va_bl_cough	Any coughing with blood	0 no, 1 yes	- " -
va_rapid_br	Any rapid breathing	0 no, 1 yes	- " -
va_exert_br	Any breathlessness on exertion	0 no, 1 yes	- " -
va_lying_br	Any breathlessness lying flat	0 no, 1 yes	- " -
va_chest_in	Any chest indrawing	0 no, 1 yes	- " -
va_diff_br	Any difficulty breathing	0 no, 1 yes	- " -
va_wheeze	Any wheezing	0 no, 1 yes	- " -
va_cyanosis	Any cyanosis	0 no, 1 yes	- " -
va_abd_mass	Any abdominal mass	0 no, 1 yes	- " -
va_abd_pain	Any abdominal pain	0 no, 1 yes	- " -
va_swe_abd	Any abdominal swelling	0 no, 1 yes	- " -
va_diarr_weeks	Diarrhoea duration	0 no diarrhoea 1 < 2 weeks 2 2-4 weeks 3 4+ weeks 4 had diarrhoea, duration not known	- " -
va_bl_diarr	Any diarrhoea with blood	0 no, 1 yes	- " -
va_vomiting	Any vomiting	0 no, 1 yes	- " -
va_bl_vomit	Any vomiting with blood	0 no, 1 yes	- " -
va_yellow	Any yellowness/jaundice	0 no, 1 yes	- " -
va_urine	Any abnormality of urine	0 no, 1 yes	- " -
va_uri_ret	Any urinary retention	0 no, 1 yes	- " -
va_uri_haem	Any haematuria	0 no, 1 yes	- " -
va_swe_legs	Any swelling of ankles/legs	0 no, 1 yes	- " -
va_eye_sunk	Were eyes sunken	0 no, 1 yes	- " -
va_rash	Any rash	0 no, 1 yes	- " -
va_measrash	Any measles rash	0 no, 1 yes	- " -
va_herpes	Any herpes zoster	0 no, 1 yes	- " -
va_skin	Any skin lesions/ulcers	0 no, 1 yes	- " -
va_swe_breast	Any breast lump or lesion	0 no, 1 yes	- " -
va_swe_gen	Any lump or lesion in groin or genitals	0 no, 1 yes	- " -
va_swe_lump	Any other localised lump or lesion	0 no, 1 yes	- " -
va_exc_drink	Any excessive water intake	0 no, 1 yes	- " -
va_exc_urine	Any excessive urination	0 no, 1 yes	- " -
va_exc_food	Any excessive food intake	0 no, 1 yes	- " -
va_fever_weeks	Fever duration	0 no fever 1 < 2 weeks 2 2+ weeks 3 had fever, duration not known	- " -
va_night_sw	Any excessive night sweats	0 no, 1 yes	- " -
va_swe_gland	Any enlarged/swollen glands	0 no, 1 yes	- " -
va_swe_oth	Any facial swelling	0 no, 1 yes	- " -
va_wt_loss	Any weight loss	0 no, 1 yes	- " -
va_wasting	Any severe wasting	0 no, 1 yes	Severe wasting is weight loss with other factors like anaemia, hair colour changes,

			swollen legs, burning feet; Stata code "." if question not asked or answer not known
va_anaemia	Any anaemia/paleness	0 no, 1 yes	Stata code "." if question not asked or answer not known
va_asthma	Any medical diagnosis of asthma	0 no, 1 yes	Stata code "." if no medical diagnosis
va_epilepsy	Any medical diagnosis of epilepsy	0 no, 1 yes	- " -
va_diabetes	Any medical diagnosis of diabetes	0 no, 1 yes	- " -
va_heart_dis	Any medical diagnosis of heart disease	0 no, 1 yes	- " -
va_kidney_dis	Any medical diagnosis of kidney disease	0 no, 1 yes	- " -
va_sickle	Any medical diagnosis of haemoglobinopathy	0 no, 1 yes	- " -
va_malaria	Any medical diagnosis of malaria	0 no, 1 yes	- " -
va_hiv_aids	Any medical diagnosis of HIV/AIDS	0 no, 1 yes	- " -
va_hypert	Any medical diagnosis of hypertension	0 no, 1 yes	- " -
va_tuber	Any medical diagnosis of TB	0 no, 1 yes	- " -
va_liver_dis	Any medical diagnosis of liver disease	0 no, 1 yes	- " -
va_cancer	Any medical diagnosis of cancer	0 no, 1 yes	- " -
va_stroke	Any medical diagnosis of stroke	0 no, 1 yes	- " -
va_measles	Any medical diagnosis of measles	0 no, 1 yes	- " -
va_antib_i	Was antibiotic injection required during final illness	0 no, 1 yes	Stata code "." if question not asked or answer not known
va_blood_tr	Was blood transfusion required during final illness	0 no, 1 yes	- " -
va_surgery	Any surgery just before death	0 no, 1 yes	- " -
va_disch	Was discharged from hospital very ill	0 no, 1 yes	- " -
va_vaccin	Was s/he adequately vaccinated	0 no, 1 yes	- " -
va_preg_status	Was she pregnant or did she deliver less than 6 weeks before she died	0 reported not pregnant within last 6 weeks 1 pregnant at time of death 2 delivered < 6 weeks after normal length pregnancy 3 delivered < 6 weeks after early pregnancy ending	Stata code "." if questions not asked or answers not known
va_married	Was she married/partnered at death	0 no, 1 yes	Stata code "." if question not asked or answer not known
va_ever_preg	Had she ever been pregnant	0 no, 1 yes	- " -
va_breast_fd	Was she breast feeding at death	0 no, 1 yes	- " -
va_first_p	Did she die during/just after first pregnancy	0 no, 1 yes	- " -
va_more4	Did she have more than 4 previous pregnancies	0 no, 1 yes	- " -
va_trim1	Did she die after less than 3 months of pregnancy	0 no, 1 yes	- " -
va_multip	Was this a multiple pregnancy	0 no, 1 yes	- " -

va_preg_uw	Was this pregnancy unwanted	0 no, 1 yes	- " -
va_term_att	Any attempt to terminate this pregnancy	0 no, 1 yes	- " -
va_hyster	Hysterectomy shortly before death	0 no, 1 yes	- " -
va_death_24	Death within 24 hrs of pregnancy ending	0 no, 1 yes	- " -
va_bleed_1	Major bleeding during early pregnancy	0 no, 1 yes	- " -
va_bleed_d	Major bleeding in late pregnancy/delivery	0 no, 1 yes	- " -
va_placent_r	Did placenta remain inside	0 no, 1 yes	- " -
va_bpr_preg	Was blood pressure raised during pregnancy	0 no, 1 yes	- " -
va_fit_preg	Were fits only pregnancy-related	0 no, 1 yes	- " -
va_baby_al	Did she deliver a live baby within 6 wks of death	0 no, 1 yes	- " -
va_lab_24	Was labour prolonged > 24 hrs	0 no, 1 yes	- " -
va_died_lab	Did she die in labour undelivered	0 no, 1 yes	- " -
va_delivery	Where did delivery take place	0 at home 1 in transit 2 at health facility	- " -
va_prof_ass	Had professional assistance at delivery	0 no, 1 yes	- " -
va_del_method	How was the baby delivered?	0 normal vaginal delivery, no instruments 1 vaginal delivery with forceps / Ventuse 2 delivery by Caesarean section	- " -
va_baby_pos	Was baby's delivery position abnormal	0 no, 1 yes	- " -
va_baby_big	Was baby too big for delivery	0 no, 1 yes	- " -
va_baby_part	Was part of the baby prolapsed	0 no, 1 yes	- " -
va_disch_sm	Any foul smelling vaginal discharge	0 no, 1 yes	- " -
va_cs_prev	Any previous Caesarean section	0 no, 1 yes	- " -
va_coma_sudden	Did the coma come on suddenly	0 no, 1 yes	Stata code "." if question not asked or answer not known
va_transport_road	Was s/he in a road transport accident	0 no, 1 yes	- " -
va_transport_oth	Was s/he in a non road transport accident	0 no, 1 yes	- " -
va_burn	Was s/he burnt by heat, steam or fire	0 no, 1 yes	- " -
va_bite	Any bite or sting by an animal	0 no, 1 yes	- " -
va_poison_2	Any poisoning (not by an animal)	0 no, 1 yes	- " -
va_inj_intent	Was h/she intentionally injured by another person or people	0 no, 1 yes	- " -
va_nature	Was s/he injured by a force of nature	0 no, 1 yes	- " -
va_assult	Injured in some kind of violence or assault by another person	0 no, 1 yes	- " -
va_convul_ti	Any convulsions or fits	0 no convulsions	- " -

me		1 < 5 minutes 2 ≥ 5 minutes 3 had convulsions, duration unknown	
va_convul_coma	Became unconscious immediately after convulsions	0 no, 1 yes	- " -
va_stiff_neck_time	Any stiff or painful neck	0 no stiff neck 1 < 1 week 2 ≥ 1 week 3 stiff neck, duration unknown	- " -
va_cough_long_2_wk	How long did cough last	0 no cough 1 < 2 weeks 2 ≥ 2 weeks 3 had cough, duration not known	- " -
va_whoop	Any distinctive whoop (associated with characteristic whooping sound of pertussis)	0 no, 1 yes	- " -
va_rapid_br_time	Any rapid breathing	0 no rapid breathing 1 < 2 weeks 2 ≥ 2 weeks 3 rapid breathing, duration unknown	- " -
va_breathless	Any breathlessness	0 no breathlessness 1 < 2 weeks 2 ≥ 2 weeks 3 rapid breathing, duration unknown	- " -
va_abd_prob	Any abdominal problem	0 no, 1 yes	- " -
va_abd_mas_time	Any abdominal mass	0 no abdominal mass 1 < 2 weeks 2 ≥ 2 weeks 3 abdominal mass, duration unknown	- " -
va_abd_pain_time	Any abdominal pain	0 no abdominal pain 1 < 2 weeks 2 ≥ 2 weeks 3 abdominal pain, duration unknown	- " -
va_swe_abd_time	Any abdominal swelling	0 no abdominal swelling 1 < 2 weeks 2 ≥ 2 weeks 3 abdominal swelling, duration unknown	- " -
va_swe_ankles	Any swelling of both feet/ankles	0 no, 1 yes	- " -
va_ulc_feet	Any ulcers/ abscesses or sores on the feet	0 no, 1 yes	- " -
va_ulc_oth	Any ulcers/ abscesses or sores on body, apart from feet	0 no, 1 yes	- " -
va_rash_time	Any non measles rash	0 no non measles rash 1 < 1 week 2 ≥ 1 week 3 non measles rash, duration unknown	- " -
va_swe	Any localised lump or lesion	0 no, 1 yes	- " -
va_swe_mouth	Any lump or lesion in mouth	0 no, 1 yes	- " -
va_swe_armpit	Any lump or lesion in armpit	0 no, 1 yes	- " -

va_swe_neck	Any lumps/swelling in neck	0 no, 1 yes	- " -
va_drink_diff	Any difficulty or pain in swallowing liquids	0 no, 1 yes	- " -
va_malaria_pos	Positive malaria test within one week of death	0 no, 1 yes	- " -
va_malaria_neg	Negative malaria test within one week of death	0 no, 1 yes	- " -
va_copd	Any medical diagnosis of chronic obstructive pulmonary disease	0 no, 1 yes	- " -
va_depress	Any medical diagnosis of depression	0 no, 1 yes	- " -
va_dementia	Any medical diagnosis of dementia	0 no, 1 yes	- " -
va_confusion	Any medical diagnosis of memory loss or mental confusions	0 no, 1 yes	- " -
va_confuse_3	Did the symptoms of mental confusion last 3 months or more?	0 no, 1 yes	- " -
va_bleed	Was the any bleeding from mouth, nose and anus	0 no, 1 yes	- " -
va_menstrual	Was there any bleeding between menstrual periods (women aged 12-50 only)	0 no, 1 yes	- " -
va_ menstr_stop	Had the woman's normal vaginal bleeding stopped naturally (women 40+)	0 no, 1 yes	- " -
va_menstr_post	Had the woman's normal vaginal bleeding stopped naturally but they later experienced vaginal bleeding	0 no, 1 yes	- " -
va_treatment	Treatment for final illness from a health facility	0 no, 1 yes	- " -
va_rehydrat	Was oral rehydration required during final illness	0 no, 1 yes	- " -
va_nose	Was treatment/food required through nose during final illness	0 no, 1 yes	- " -
va_iv	Was an IV drip required during final illness	0 no, 1 yes	- " -
va_operation	Was there an operation within one month of death	0 no, 1 yes	- " -
va_early_preg	Was the woman at an early stage of pregnancy within 6 weeks of her death, but the pregnancy had ended in a spontaneous or induced abortion at a stage before the foetus was viable?	0 no, 1 yes	- " -
va_rec_abort	Any recent abortion	0 no, 1 yes	- " -
va_bleed_m	Mother had excessive vaginal bleeding in pregnancy/postpartum period	0 no, 1 yes	- " -
va_bleed_preg	Major bleeding in first 6 months of pregnancy	0 no, 1 yes	- " -

va_bleed_pre_lab	Major bleeding shortly before labour	0 no, 1 yes	- " -
va_bleed_lab	Major bleeding during labour, before delivering the baby	0 no, 1 yes	- " -
va_bleed_post_lab	Major bleeding after delivering the baby	0 no, 1 yes	- " -
va_vis_bl_preg	Any blurred vision during the last 3 months of preg	0 no, 1 yes	- " -

Appendix D Supplementary Tables

Supplementary Table 1: Detailed look at how the key symptoms in ALPHA specification are produce from the verbal autopsy questionnaires in Karonga and Kisesa

	Kisesa				Karonga	
	% missing data	**VA questionnaire 1994-2002: TANESA questionnaire**	**VA questionnaire 2002-2007: INDEPTH questionnaire**	**VA questionnaire 2007-2011: TAZAMA questionnaire**	**% missing data**	**VA questionnaire version 11**
HIV SYMPTOMS						
Any medical diagnosis of HIV/AIDS	16.6	Was (NAME) known to have HIV infection?	Did the deceased suffer from any of the following illness? Option: HIV/AIDS	Please tell me if the deceased suffer from any other following: HIV/AIDS	43.6	Did s/he have HIV/AIDs? OR Had s/he ever had an HIV test? What was the most recent results? Option: Pos
Any weight loss	4.8	During the disease that led to death did (NAME) lose weight?	Had s/he lost weight recently before death?	Did s/he have weight loss?	1.3	Has s/he lost weight recently before death?
Any severe wasting	16.3	During the disease that led to death did (NAME) lose weight? Was the weight loss severe or moderate?	Had s/he lost weight recently before death? Was the weight loss? Option: Severe (a lot)	Did s/he have weight loss? Did s/he look very thin and wasted?	47.9	Was the weight loss severe?
Any abnormal hair colouring	54.4	Did the colour of the hair change?	**NO QUESTION**	**NO QUESTION**	89.6	Did s/he have changing colour hair?
Any swelling of the legs	6.8	During the disease that led to death did (NAME) have swollen legs?	Had s/he have swelling around the ankle?	Did s/he have any swelling? Was the swelling on? Option: The ankles	3.7	Did s/he have swelling around the ankles?
Any anaemia/ paleness	3.4	During the disease that led to death did (NAME) become very pale?	Did s/he look pale (anaemic)?	Did s/he look pale (thinning/lack of blood) or have pale palms, eyes or nail beds?	4.3	Did s/he look pale (anaemic)?
Any yellowness/ jaundice	3.6	During the disease that led to death did (NAME) yellowing of the white of the eyes (jaundice)? OR Did (NAME) have attacks of becoming yellow during his/her life?	Did s/he have yellow discolouration of the eyes?	Did s/he have yellow discolouration of the eyes?	1.3	Did s/he have yellow discoloration of the eyes?
How long did fever last?	0	Did (NAME) have fever? For how long?	During the illness that led to death did s/he have fever? How many days did s/he have fever?	Did s/he have fever? For how long did s/he have fever?	4.0	Did s/he have fever? How many days did s/he have fever?

	Kisesa				Karonga	
	% missing data	**VA questionnaire 1994-2002: TANESA questionnaire**	**VA questionnaire 2002-2007: INDEPTH questionnaire**	**VA questionnaire 2007-2011: TAZAMA questionnaire**	**% missing data**	**VA questionnaire version 11**
Any herpes zoster	17.9	Has (NAME) ever had herpes zoster?	Did s/he ever have herpes zoster before death?	Did s/he ever have shingles/herpes zoster?	85.8	Did s/he ever have shingles (past or present probe)
Any oral candidiasis	14.7	Did (NAME) have white patches on the inside of the mouth and tongue?	**NO QUESTION**	Did s/he have mouth sores or white patches in the mouth or on the tongue?	75.1	Did s/he have oral candidiasis?
Any ulcers/ abscesses or sores on the feet	62.8	**NO QUESTION**	Did s/he have ulcer on any part of the body? If yes, please specify	Did s/he have an ulcer, abscess or sores anywhere on the body? What was the location of the ulcer, abscess or sore? Option: Other parts of body, specify	100	**NO QUESTION**
Any ulcers/ abscesses or sores on body, apart from feet	5.9	**NO QUESTION**	Did s/he have ulcer on any part of the body? If yes, please specify	Did s/he have an ulcer, abscess or sores anywhere on the body?	100	**NO QUESTION**
Any difficulty breathing	49.0	Did (NAME) have trouble breathing during the illness that lead to death?	**NO QUESTION**	**NO QUESTION**	100	**NO QUESTION**
How long did cough last?	2.7	Did (NAME) have a cough? For how long?	Did s/he have cough? How many days did s/he have cough?	For how long did s/he have a cough?	1.9	Did s/he have cough? How many days did s/he have a cough?
Any medical diagnosis of TB	51.9	Did (NAME) ever have tuberculosis?	Did the deceased suffer from any of the following illness? Option: TB	Please tell me if the deceased suffer from any of the following: Tuberculosis	3.5	Did s/he have tuberculosis?
Any lump or lesion in groin or genitals	6.1	Did (NAME) have swellings? Which parts were swollen? Option: Groin OR Did (NAME) have a swelling growing out of the vagina?	Did s/he have swelling in the groin?	Did s/he have any swelling? Was the swelling on? Option: Other place, specify OR Did she have any lumps? Were the lumps on? Option: The groin	5.1	Did s/he have swelling in the groin?
How long did diarrhoea last?	2.3	Did (NAME) have frequent loose stools or liquid stools during the disease that led to death? For how long did the diarrhoea last?	Did s/he have diarrhoea? How many days did she have diarrhoea?	Did s/he have diarrhoea? For how long did s/he have diarrhoea?	1.1	Did s/he have diarrhoea? How many days did s/he have diarrhoea?
PREGNANCY SYMPTOMS						
Death within 24 hours of pregnancy ending	84.7	**NO QUESTION**	How many days before her death did she deliver	How many days after giving birth did she die?	100	How many days before her death did she deliver?
Did she die in labour undelivered	79.7	**NO QUESTION**	**NO QUESTION**	Did she die during labor, but undelivered?	0	**NO QUESTION**

	Kisesa				Karonga	
	% missing data	**VA questionnaire 1994-2002: TANESA questionnaire**	**VA questionnaire 2002-2007: INDEPTH questionnaire**	**VA questionnaire 2007-2011: TAZAMA questionnaire**	**% missing data**	**VA questionnaire version 11**
INJURY SYMPTOMS						
Any obvious recent injury	5.9	During the two weeks before (NAME) died, did he/she suffer from any major injury, poisoning, burn or drowning?	Did s/he sustain any injury which led to his/her death?	Did s/he suffer from any injury or accident that lead to her/his death?	98.7	Did s/he sustain any injury which lead to his/her death?
Was s/he in a transport accident	49.9	During the two weeks before (NAME) died, did he/she suffer from any major injury, poisoning, burn or drowning? Option: Motor vehicle accident	Did s/he sustain any injury which led to his/her death? If yes ask What kind of injury or accident? Option: Transport accident (pedestrian), Transport accident (passenger/driver)	Did s/he suffer from any injury or accident that lead to her/his death? What kind of injury or accident did the deceased suffer: Road traffic accident	1.3	Did s/he sustain any injury which lead to his/her death? If yes probe for type of injury. Option: Road traffic accident
Did s/he drown	49.9	During the two weeks before (NAME) died, did he/she suffer from any major injury, poisoning, burn or drowning? Option: Drowning	Did s/he sustain any injury which led to his/her death? If yes ask What kind of injury or accident? Option: Drowning	Did s/he suffer from any injury or accident that lead to her/his death? What kind of injury or accident did the deceased suffer: Drowning	3.2	Did s/he sustain any injury which lead to his/her death? If yes probe for type of injury. Option: Other, specify
Had s/he fallen recently	49.9	During the two weeks before (NAME) died, did he/she suffer from any major injury, poisoning, burn or drowning? Option: Fall	Did s/he sustain any injury which led to his/her death? If yes ask, What kind of injury or accident? Option: Fall	Did s/he suffer from any injury or accident that lead to her/his death? What kind of injury or accident did the deceased suffer: Fall	1.3	Did s/he sustain any injury which lead to his/her death? If yes probe for type of injury. Option: Other, specify
Was s/he burnt by heat steam or fire	51.7	During the two weeks before (NAME) died, did he/she suffer from any major injury, poisoning, burn or drowning? Option: Burn	Did s/he sustain any injury which led to his/her death? If yes ask, What kind of injury or accident? Option: Burn	Did s/he suffer from any injury or accident that lead to her/his death? What kind of injury or accident did the deceased suffer? Option: Burns	1.3	Did s/he sustain any injury which lead to his/her death? Type of injury - Option: Fire accident
Any poisoning, bite, sting	49.9	During the two weeks before (NAME) died, did he/she suffer from any major injury, poisoning, burn or drowning? Option: Poisoning	Did s/he sustain any injury which led to his/her death? If yes ask, What kind of injury or accident? Option: Poisoning, Animal bite, Other bite or sting	What kind of injury or accident did the deceased suffer: Poisoning OR Did s/he suffer from any animal/insect bit that led to her/his death?	1.3	Did s/he sustain any injury which lead to his/her death? If yes probe for type of injury. Option: Animal bite, Accidental poisoning
Was s/he intentionally injured by another person or people	44.0	Was it an accident, was it inflicted deliberately by someone else, or was the death self-inflicted? Option Homicide	**NO QUESTION**	Was the injury or accident intentionally inflicted by someone else?	100	**NO QUESTION**

	Kisesa				Karonga	
	% missing data	**VA questionnaire 1994-2002: TANESA questionnaire**	**VA questionnaire 2002-2007: INDEPTH questionnaire**	**VA questionnaire 2007-2011: TAZAMA questionnaire**	**% missing data**	**VA questionnaire version 11**
Was s/he injured by a force of nature	100	**NO QUESTION**	**NO QUESTION**	**NO QUESTION**	100	**NO QUESTION**
Injured in some kind of violence or assault by another person	51.7	**NO QUESTION**	Did s/he sustain any injury which led to his/her death? If yes ask What kind of injury or accident? Option: Assault/abuse	Did s/he suffer from any injury or accident that lead to her/his death? What kind of injury or accident did the deceased suffer? Option: Violence/assault	1.3	Did s/he sustain any injury which lead to his/her death? If yes probe for type of injury. Option: Other, specify OR Assault
Any suggestion of homicide	31.5	Was it an accident, was it inflicted by someone else, or self-inflicted? Option: Homicide	**NO QUESTION**	Was the injury or accident intentionally inflicted by someone else? OR What kind of injury or accident did the deceased suffer: Violence/assault	98.4	Did s/he sustain any injury which lead to his/her death? If yes probe for type of injury. Option: Other, specify OR Assault
Any suggestion of suicide	32.7	Was it an accident, was it inflicted by someone else, or self-inflicted? Option: Suicide	Do you think s/he committed suicide?	Do you think that s/he committed suicide?	2.1	Do you think that s/he committed suicide?

Supplementary Table 2: Percentage of women of reproductive age missing data for each VA symptom

	Karonga (N=374) N (%)	Kisesa (N=441) N (%)	uMkhanyakude (N=2680) N (%)	All sites (N=3,495) N (%)
Was she pregnant or did she deliver less than 6 weeks before she died	0 (0)	165 (37.4)	979 (36.5)	1144 (32.7)
Was she married/partnered at death	374 (100)	233 (52.8)	1964 (73.3)	2571 (73.6)
Had she ever been pregnant	374 (100)	388 (88.0)	2680 (100)	3442 (98.5)
Was she breast feeding at death	374 (100)	441 (100)	2680 (100)	3495 (100)
Did she die during/just after first pregnancy	374 (100)	222 (50.3)	2680 (100)	3276 (93.7)
Did she have more than 4 previous pregnancies	374 (100)	212 (48.1)	2680 (100)	3266 (93.4)
Did she die after less than 3 months of pregnancy	30 (8.0)	244 (55.3)	11 (0.4)	285 (8.2)
Was this a multiple pregnancy	374 (100)	441 (100)	2680 (100)	3495 (100)
Was this pregnancy unwanted	374 (100)	441 (100)	2680 (100)	3495 (100)
Any attempt to terminate this pregnancy	374 (100)	245 (55.6)	2680 (100)	3299 (94.4)
Hysterectomy shortly before death	374 (100)	441 (100)	2680 (100)	3495 (100)
Major bleeding during early pregnancy	374 (100)	290 (65.8)	2680 (100)	3344 (95.7)
Major bleeding in late pregnancy/delivery	356 (95.2)	289 (65.5)	2680 (100)	3325 (95.1)
Did placenta remain inside	374 (100)	422 (95.7)	2664 (99.4)	3460 (99.0)
Was blood pressure raised during pregnancy	328 (87.7)	415 (94.1)	1798 (67.1)	2541 (72.7)
Were fits only pregnancy-related	374 (100)	430 (97.5)	1723 (64.3)	2527 (72.3)
Did she deliver a live baby within 6 wks of death	349 (93.3)	427 (96.8)	2680 (100)	3456 (98.9)
Was labour prolonged > 24 hrs	374 (100)	430 (97.5)	11 (0.4)	815 (23.3)
Where did delivery take place	345 (92.2)	303 (68.7)	2680 (100)	3328 (95.2)
Had professional assistance at delivery	374 (100)	432 (98.0)	2680 (100)	3486 (99.7)
How was the baby delivered?	347 (92.8)	429 (97.3)	2680 (100)	3456 (98.9)
Was baby's delivery position abnormal	374 (100)	441 (100)	2680 (100)	3495 (100)
Was baby too big for delivery	374 (100)	441 (100)	2680 (100)	3495 (100)
Was part of the baby prolapsed	374 (100)	441 (100)	2680 (100)	3495 (100)
Any foul smelling vaginal discharge	374 (100)	432 (98.0)	558 (20.8)	1364 (39.0)
Any previous Caesarean section	374 (100)	441 (100)	2680 (100)	3495 (100)
Was the woman at an early stage of pregnancy within 6 weeks of her death, but the pregnancy had ended in a spontaneous or induced abortion at a stage before the foetus was viable?	374 (100)	244 (55.3)	2680 (100)	3298 (94.4)
Any recent abortion	44 (11.8)	243 (55.1)	1748 (65.2)	2035 (58.2)
Mother had excessive vaginal bleeding in pregnancy/postpartum period	356 (95.2)	131 (29.7)	1790 (66.8)	2277 (65.2)
Major bleeding in first 6 months of pregnancy	374 (100)	419 (95.0)	1790 (66.8)	2583 (73.9)

	Karonga (N=374) N (%)	Kisesa (N=441) N (%)	uMkhanyakude (N=2680) N (%)	All sites (N=3,495) N (%)
Major bleeding shortly before labour	374 (100)	422 (95.7)	2680 (100)	3476 (99.5)
Major bleeding during labour, before delivering the baby	356 (95.2)	433 (98.2)	2680 (100)	3469 (99.3)
Major bleeding after delivering the baby	356 (95.2)	434 (98.4)	2680 (100)	3470 (99.3)
Any blurred vision during the last 3 months of preg	374 (100)	430 (97.5)	2680 (100)	3484 (99.7)
Did final illness last at least 3 weeks?	374 (100)	78 (17.7)	3 (0.1)	455 (13.0)
Was death very sudden or unexpected	374 (100)	52 (11.8)	55 (2.1)	481 (13.8)
Any blurred vision	374 (100)	283 (64.2)	2680 (100)	3337 (95.5)
Any drowsiness	374 (100)	441 (100)	2680 (100)	3495 (100)
Was bed-bound for more than 1wk before death	374 (100)	441 (100)	2680 (100)	3495 (100)
Was there a coma > 24hrs	10 (2.7)	72 (16.3)	3 (0.1)	85 (2.4)
Did death follow sudden collapse	374 (100)	393 (89.1)	2680 (100)	3447 (98.6)
Season of death	0 (0)	103 (23.4)	0 (0.0)	103 (2.9)
Was s/he a known smoker	374 (100)	230 (52.2)	4 (0.1)	608 (17.4)
Was s/he known to drink alcohol	374 (100)	30 (6.8)	5 (0.2)	409 (11.7)
Any convulsions or fits	6 (1.6)	374 (84.8)	13 (0.5)	393 (11.2)
Any headache	10 (2.7)	179 (40.6)	687 (25.6)	876 (25.1)
Was there paralysis	7 (1.9)	21 (4.8)	617 (23.0)	645 (18.5)
Any stiff neck	27 (7.2)	5 (1.1)	673 (25.1)	705 (20.2)
Any rigidity/lockjaw	0 (0)	55 (12.5)	639 (23.8)	694 (19.9)
Any chest pain	11 (2.9)	177 (40.1)	297 (11.1)	485 (13.9)
Any productive cough	15 (4.0)	227 (51.5)	1 (0)	243 (7.0)
Any coughing with blood	19 (5.1)	229 (51.9)	99 (3.7)	347 (9.9)
Any rapid breathing	13 (3.5)	113 (25.6)	8 (0.3)	134 (3.8)
Any breathlessness on exertion	144 (38.5)	299 (67.8)	660 (24.6)	1103 (31.6)
Any breathlessness lying flat	374 (100)	317 (71.9)	2663 (99.4)	3354 (96.0)
Any chest indrawing	374 (100)	441 (100)	8 (0.3)	823 (23.5)
Any wheezing	216 (57.8)	388 (88.0)	199 (7.4)	803 (23.0)
Any cyanosis	374 (100)	441 (100)	2680 (100)	3495 (100)
Any abdominal mass	29 (7.8)	257 (58.3)	660 (24.6)	946 (27.1)
Any abdominal pain	9 (2.4)	205 (46.5)	1323 (49.4)	1537 (44.0)
Any abdominal swelling	4 (1.1)	42 (9.5)	626 (23.4)	672 (19.2)
Any diarrhoea with blood	25 (6.7)	266 (60.3)	8 (0.3)	299 (8.6)
Any vomiting	9 (2.4)	14 (3.2)	210 (7.8)	233 (6.7)
Any vomiting with blood	219 (58.6)	210 (47.6)	210 (7.8)	639 (18.3)
Any abnormality of urine	30 (8.0)	60 (13.6)	11 (0.4)	101 (2.9)
Any urinary retention	27 (7.2)	160 (36.3)	9 (0.3)	196 (5.6)
Any haematuria	24 (6.4)	114 (25.9)	11 (0.4)	149 (4.3)
Were eyes sunken	374 (100)	326 (73.9)	672 (25.1)	1372 (39.3)
Any rash	9 (2.4)	15 (3.4)	10 (0.4)	34 (1.0)
Any measles rash	59 (15.8)	268 (60.8)	11 (0.4)	338 (9.7)
Any skin lesions/ulcers	237 (63.4)	22 (5.0)	9 (0.3)	268 (7.7)

	Karonga (N=374) N (%)	Kisesa (N=441) N (%)	uMkhanyakude (N=2680) N (%)	All sites (N=3,495) N (%)
Any breast lump or lesion	19 (5.1)	232 (52.6)	549 (20.5)	800 (22.9)
Any other localised lump or lesion	7 (1.9)	78 (17.7)	327 (12.2)	412 (11.8)
Any excessive water intake	374 (100)	243 (55.1)	2656 (99.1)	3273 (93.6)
Any excessive urination	27 (7.2)	152 (34.5)	11 (0.4)	190 (5.4)
Any excessive food intake	374 (100)	441 (100)	2680 (100)	3495 (100)
Any excessive night sweats	351 (93.9)	270 (61.2)	617 (23.0)	1238 (35.4)
Any enlarged/swollen glands	13 (3.5)	82 (18.6)	2680 (100)	2775 (79.4)
Any facial swelling	6 (1.6)	62 (14.1)	2680 (100)	2748 (78.6)
Any medical diagnosis of asthma	307 (82.1)	229 (51.9)	11 (0.4)	547 (15.7)
Any medical diagnosis of epilepsy	1 (0.3)	228 (51.7)	108 (4.0)	337 (9.6)
Any medical diagnosis of diabetes	6 (1.6)	18 (4.1)	10 (0.4)	34 (1.0)
Any medical diagnosis of heart disease	374 (100)	187 (42.4)	104 (3.9)	665 (19.0)
Any medical diagnosis of kidney disease	374 (100)	441 (100)	104 (3.9)	919 (26.3)
Any medical diagnosis of haemoglobinopathy	374 (100)	241 (54.6)	2680 (100)	3295 (94.3)
Any medical diagnosis of malaria	374 (100)	416 (94.3)	105 (3.9)	895 (25.6)
Any medical diagnosis of hypertension	5 (1.3)	23 (5.2)	2 (0.1)	30 (0.9)
Any medical diagnosis of liver disease	374 (100)	441 (100)	103 (3.8)	918 (26.3)
Any medical diagnosis of cancer	374 (100)	275 (62.4)	100 (3.7)	749 (21.4)
Any medical diagnosis of stroke	374 (100)	441 (100)	1 (0.0)	816 (23.3)
Any medical diagnosis of measles	374 (100)	441 (100)	2663 (99.4)	3478 (99.5)
Was antibiotic injection required during final illness	374 (100)	396 (89.8)	2680 (100)	3450 (98.7)
Was blood transfusion required during final illness	374 (100)	298 (67.6)	2680 (100)	3352 (95.9)
Any surgery just before death	4 (1.1)	235 (53.3)	66 (2.5)	305 (8.7)
Was discharged from hospital very ill	374 (100)	441 (100)	2667 (99.5)	3482 (99.6)
Was s/he adequately vaccinated	374 (100)	441 (100)	2678 (99.9)	3493 (99.9)
Did the coma come on suddenly	0 (0)	386 (87.5)	2667 (99.5)	3053 (87.4)
Any convulsions or fits	6 (1.6)	395 (89.6)	13 (0.5)	414 (11.8)
Became unconscious immediately after convulsions	374 (100)	441 (100)	11 (0.4)	826 (23.6)
Any stiff or painful neck	27 (7.2)	30 (6.8)	673 (25.1)	730 (20.9)
How long did cough last	7 (1.9)	12 (2.7)	91 (3.4)	110 (3.1)
Any distinctive whoop (associated with characteristic whooping sound of pertussis)	374 (100)	441 (100)	2680 (100)	3495 (100)
Any rapid breathing	374 (100)	441 (100)	8 (0.3)	823 (23.5)
Any breathlessness	13 (3.5)	125 (28.3)	1 (0)	139 (4.0)
Any abdominal problem	374 (100)	40 (9.1)	2680 (100)	3094 (88.5)
Any abdominal mass	29 (7.8)	260 (59.0)	660 (24.6)	949 (27.2)
Any abdominal pain	9 (2.4)	54 (12.2)	1323 (49.4)	1386 (39.7)
Any abdominal swelling	4 (1.1)	176 (39.9)	626 (23.4)	806 (23.1)
Any swelling of both feet/ankles	14 (3.7)	295 (66.9)	412 (15.4)	721 (20.6)
Any non measles rash	9 (2.4)	15 (3.4)	10 (0.4)	34 (1.0)
Any localised lump or lesion	374 (100)	20 (4.5)	327 (12.2)	721 (20.6)

	Karonga (N=374) N (%)	Kisesa (N=441) N (%)	uMkhanyakude (N=2680) N (%)	All sites (N=3,495) N (%)
Any lump or lesion in mouth	374 (100)	22 (5.0)	2680 (100)	3076 (88.0)
Any lump or lesion in armpit	14 (3.7)	174 (39.5)	530 (19.8)	718 (20.5)
Any lumps/swelling in neck	22 (5.9)	173 (39.2)	519 (19.4)	714 (20.4)
Any difficulty or pain in swallowing liquids	9 (2.4)	23 (5.2)	93 (3.5)	125 (3.6)
Positive malaria test within one week of death	374 (100)	441 (100)	105 (3.9)	920 (26.3)
Negative malaria test within one week of death	374 (100)	441 (100)	2680 (100)	3495 (100)
Any medical diagnosis of chronic obstructive pulmonary disease	374 (100)	441 (100)	2680 (100)	3495 (100)
Any medical diagnosis of depression	374 (100)	441 (100)	2680 (100)	3495 (100)
Any medical diagnosis of dementia	374 (100)	441 (100)	2680 (100)	3495 (100)
Any medical diagnosis of memory loss or mental confusions	374 (100)	441 (100)	2679 (100)	3494 (100)
Did the symptoms of mental confusion last 3 months or more?	374 (100)	293 (66.4)	2680 (100)	3347 (95.8)
Was the any bleeding from mouth, nose and anus	374 (100)	288 (65.3)	14 (0.5)	676 (19.3)
Was there any bleeding between menstrual periods (women aged 12-50 only)	24 (6.4)	295 (66.9)	562 (21.0)	881 (25.2)
Had the woman's normal vaginal bleeding stopped naturally (women 40+)	374 (100)	246 (55.8)	2680 (100)	3300 (94.4)
Had the woman's normal vaginal bleeding stopped naturally but they later experienced vaginal bleeding	374 (100)	307 (69.6)	2680 (100)	3361 (96.2)
Treatment for final illness from a health facility	374 (100)	84 (19.0)	3 (0.1)	461 (13.2)
Was oral rehydration required during final illness	374 (100)	246 (55.8)	2680 (100)	3300 (94.4)
Was treatment/food required through nose during final illness	374 (100)	300 (68.0)	2680 (100)	3354 (96.0)
Was an IV drip required during final illness	374 (100)	441 (100)	2680 (100)	3495 (100)
Was there an operation within one month of death	4 (1.1)	232 (52.6)	2680 (100)	2916 (83.4)

Supplementary Table 3: Cause of death using the Lopman algorithm when peripartum deaths are not included in the categorisation

	Number of deaths	Number of deaths assigned to:		
		Injuries/ Accidents (%)	HIV/AIDS (%)	Other (%)
Karonga	374	10 (2.7)	196 (52.4)	168 (44.9)
Kisesa	441	29 (6.6)	270 (61.2)	142 (32.2)
uMkhanyakude	2680	108 (4.0)	2153 (80.3)	419 (15.6)
All sites	3495	147 (4.2)	2619 (74.9)	729 (20.9)

Supplementary Table 4: Cause of death distributions assigned using the most likely cause of death from InterVA-4, stratified by HIV and region

	Number of deaths	Percentage of deaths assigned to:						
		HIV/AIDS-related death	Pulmonary tuberculosis	Other infectious diseases	Non communicable diseases	External causes of death	Direct obstetric causes	No primary cause assigned
Karonga	374	35.3	15.0	23.5	15.8	2.1	7.0	1.3
Kisesa	441	42.6	8.2	8.2	24.7	4.3	10.4	1.6
uMkhanyakude	2680	32.4	46.4	4.7	9.9	3.5	1.6	1.3
All sites	3495	34.0	38.2	7.2	12.4	3.5	3.3	1.4

Supplementary Table 5: Cause of death using the Lopman algorithm, by pregnancy and HIV status

		Number of deaths	Number of deaths assigned to:			
			Injuries/ Accidents (%)	Peripartum (%)	HIV/AIDS (%)	Other (%)
Karonga						
Pregnant or up to 42 days postpartum	HIV negative	22	1 (4.5)	5 (22.7)	2 (9.1)	14 (63.6)
	HIV positive	7	0 (0)	1 (14.3)	1 (14.3)	5 (71.4)
	HIV status unknown	18	0 (0)	4 (22.2)	1 (5.6)	13 (72.2)
	Overall	47	1 (2.1)	10 (21.3)	4 (8.5)	32 (68.1)
Not pregnant or up to 42 days postpartum	HIV negative	42	4 (9.5)	0 (0)	14 (33.3)	24 (57.1)
	HIV positive	162	1 (0.6)	0 (0)	107 (66.0)	54 (33.3)
	HIV status unknown	123	4 (3.3)	0 (0)	70 (56.9)	49 (39.8)
	Overall	327	9 (2.8)	0 (0)	191 (58.4)	127 (38.8)
Kisesa						
Pregnant or up to 42 days postpartum	HIV negative	28	1 (3.6)	3 (10.7)	7 (25.0)	17 (60.7)
	HIV positive	9	0 (0)	0 (0)	6 (66.7)	3 (33.3)
	HIV status unknown	22	0 (0)	2 (9.1)	6 (27.3)	14 (63.6)
	Overall	59	1 (1.7)	5 (8.5)	19 (32.2)	34 (57.6)
Not pregnant or up to 42 days postpartum	HIV negative	87	13 (14.9)	0 (0)	40 (46.0)	34 (39.1)
	HIV positive	132	2 (1.5)	0 (0)	114 (86.4)	16 (12.1)
	HIV status unknown	163	13 (8.0)	0 (0)	97 (59.5)	53 (32.5)
	Overall	382	28 (7.3)	0 (0)	251 (65.7)	103 (27.0)
uMkhanyakude						
Pregnant or up to 42 days postpartum	HIV negative	3	0 (0)	0 (0)	1 (33.3)	2 (66.7)
	HIV positive	26	1 (3.8)	0 (0)	16 (61.5)	9 (34.6)
	HIV status unknown	42	1 (2.4)	0 (0)	13 (31.0)	28 (66.7)
	Overall	71	2 (2.8)	0 (0)	30 (42.3)	39 (54.9)
Not pregnant or up to 42 days postpartum	HIV negative	51	12 (23.5)	0 (0)	20 (39.2)	19 (37.3)
	HIV positive	1044	19 (1.8)	0 (0)	923 (88.4)	102 (9.8)
	HIV status unknown	1514	75 (5.0)	0 (0)	1180 (77.9)	259 (17.1)
	Overall	2609	106 (4.1)	0 (0)	2123 (81.4)	380 (14.6)

Supplementary Table 6: Cause of death distributions assigned using InterVA-4, stratified by site, HIV and pregnancy status

		Number of deaths	Percentage of deaths assigned to:					
			HIV/ AIDS	Pulmonary TB	Other infectious diseases	Non communicable diseases	External causes	Direct obstetric causes
Karonga								
Pregnant or up to 42 days postpartum	HIV negative	22	0.6	3.7	25.2	7	2.1	61.3
	HIV positive	7	14.5	0	14.5	28.1	0	42.9
	HIV status unknown	18	5.6	0	16.6	21.7	0	56.1
	Overall	47	4.6	1.7	20.3	15.8	1.0	56.6
Not pregnant or up to 42 days postpartum	HIV negative	42	15.6	15.8	35.7	20.4	12.5	0
	HIV positive	162	48.5	19.6	21.2	10.4	0.3	0
	HIV status unknown	123	36.2	12.5	26.1	20.4	4.8	0
	Overall	327	39.6	16.5	24.9	15.5	3.5	0
Kisesa								
Pregnant or up to 42 days postpartum	HIV negative	28	14.4	3.8	3.5	15.3	0	62.9
	HIV positive	9	36.9	0	0.4	24.4	0	38.3
	HIV status unknown	22	14.6	4.7	0.5	11.6	0	68.6
	Overall	59	17.9	3.5	1.9	15.3	0	61.3
Not pregnant or up to 42 days postpartum	HIV negative	87	23.2	7.1	14.9	37.9	12.2	4.7
	HIV positive	132	65	10.2	6.5	16.6	0	1.7
	HIV status unknown	163	42.3	9.4	10.3	29.1	6.3	2.6
	Overall	382	45.8	9.1	10	26.8	5.5	2.8
uMkhanyakude								
Pregnant or up to 42 days postpartum	HIV negative	3	0.8	0	32.6	0	0	66.6
	HIV positive	26	41.5	24.2	4.5	8.4	0	21.4
	HIV status unknown	42	24.7	8	2	19.5	4.4	41.4

	Overall	71	29.8	13.6	4.2	14.6	2.6	35.2
Not pregnant or up to 42 days postpartum	HIV negative	51	18.4	19.9	4.7	31.6	23.3	2.1
	HIV positive	1044	37.3	49.5	3.8	7.3	1.8	0.2
	HIV status unknown	1514	29.2	47.2	5.7	11.9	4.7	1.2
	Overall	2609	32.3	47.6	4.9	10.5	3.9	0.8