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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)

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Summary

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 post-partum 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 post partum were defined as pregnancy related. Pregnant or post-partum 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 post-partum women and women who were not pregnant or post partum.

Findings 138 074 women aged 15–49 years contributed 636 213 person-years of observation. 49 568 women had 86 963 pregnancies. 6760 of these women died, 235 of them during pregnancy or the post-partum period. Mean prevalence of HIV infection across all person-years in the pooled data was 17·2% (95% CI 17·0–17·3), but 60 of 118 (50·8%) of the women of known HIV status who died during pregnancy or post partum were HIV infected. The mortality rate ratio of HIV-infected to HIV-uninfected women was 20·5 (18·9–22·4) in women who were not pregnant or post partum and 8·2 (5·7–11·8) in pregnant or post-partum women. Excess mortality attributable to HIV was 51·8 (47·8–53·8) per 1000 person-years in women who were not pregnant or post partum and 11·8 (8·4–15·3) per 1000 person-years in pregnant or post-partum women.

Interpretation HIV-infected pregnant or post-partum 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 post-partum 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 post-partum women.

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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—ie, to halve HIV mortality in pregnant or post-partum women by 2015.¹ The substantial increase in adult mortality because of HIV, which has been noted in many studies in sub-Saharan Africa,^{2,3} 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.^{4,5} In Zimbabwe, the maternal mortality ratio increased by a factor of 2·5 between 1985 and 1994, and in Malawi it increased by a factor of 1·8 between 1995 and 1999.⁶ Reasons for these increases are poorly understood. The increasing prevalence of HIV infection is thought to be the main driver,^{4,5} 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 review⁷ of

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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). Most studies that have been published so far are facility based. Some hospital-based studies^{8–11} 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,⁹ and, in a 2012 analysis¹² 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 post-partum women should be classified as maternal; as a result, roughly 20·5% of maternal deaths in 2011 were attributed to HIV globally.⁵ 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 post-partum 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.⁴

An alternative measure of the contribution of HIV to mortality during pregnancy is the excess mortality associated with HIV in pregnant or post-partum women. On the basis of a systematic review¹³ of 23 studies, 17 of which were done in sub-Saharan Africa, HIV-infected pregnant or post-partum women were estimated to have nearly eight times the risk of death that non-HIV-infected women had. 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 studies¹⁴ from eastern and southern Africa (six of which have the necessary data), to calculate the excess mortality associated with HIV during pregnancy and the post-partum period.

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.^{15–20} 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.^{21–26} 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 dataset 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 dataset, so that all data met the same validity and consistency criteria 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 post-partum women (up to 42 days' post partum). 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.²⁷ 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.^{28,29} We used only two sets of responses in this analysis—those to questions about whether the woman was pregnant or post partum 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,³⁰ we classified death as pregnancy related if it occurred while the woman was pregnant or post partum, 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' post-partum 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—ie, 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 uMmkhanyukude. 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 (eg, 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

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Location	Karonga	Kisesa	Manicaland	Masaka	Rakai	uMkhanyukude
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 (%)	12%	5%	24%	7%	16%	22%
Prevalence of HIV infection* at end date (%)	8%	6%	14%	9%	11%	29%
Population at start date (n)	31 000	20 000	15 000	8000	30 000	93 000
Population at end date (n)	35 000	34 000	37 000	19 000	40 000	96 000
Frequency of 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	2003–12	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

Populations are rough estimates; numbers are rounded for ease of comparison. ART=antiretroviral therapy. *In people aged 15 years or older.

Table 1: Characteristics of Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA) study sites contributing data for HIV and maternal mortality

established to be HIV infected on the basis of verbal autopsies had been infected for 5 years—ie, half the median postinfection survival time in the pooled dataset.¹⁷

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 1000 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 post-partum women and for those who were not pregnant or post partum. For the pooled dataset, we used Mantel-Haenzel 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—ie, 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 post-partum women in the pooled ALPHA dataset, we used the standard relation:³¹

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

Results

Table 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 2). 49 568 women had 86 963 pregnancies; HIV status was known during 49 740 (57·2%) of these pregnancies. 6760 deaths were reported in women of reproductive age, of which 3709 (54·9%) could be classified by HIV status (table 3). Of the 235 of these deaths that were in women who were pregnant or post partum, HIV status was known for 118 (50·2%; table 3).

The overall mean prevalence of HIV infection during the data collection period in the pooled dataset was 17·2% (95% CI 17·0–17·3). Prevalence in pregnant or post-partum women (11·2% [10·9–11·5]) was significantly lower than that in women who were not pregnant or post partum (18·0% [17·9–18·1]; p<0·0001). The appendix shows the prevalence of HIV infection in women of reproductive age by year. Mean prevalence was 7·2% (7·0–7·4) in Kisesa, 8·2% (7·9–8·4) in Masaka, 9·6% (9·2–10·0) in Karonga, 15·7% (15·5–15·9) in Rakai, 24·5% (24·0–25·0) in Manicaland, and 35·4% (35·0–35·8) in uMkhanyakude. Mean prevalence in women who were pregnant or post partum was significantly lower than that in women who were not pregnant or post partum (data not shown).

The general fertility rate in the pooled dataset was 132 (95% CI 131–133) births per thousand person-years. Fertility rates were significantly lower in HIV-infected women (100 [97–104]) than in HIV-uninfected women (172 [170–174]; p<0·0001). General fertility rates were lower in the southern African sites—ie, Manicaland (85·8 [82·5–89·1]) and uMkhanyakude (98·2 [96·9–99·5])—than in the east African sites—ie, Karonga (190·5 [187·1–194·0]), Kisesa (180·6 [177·9–183·4]), Masaka (157·9 [154·7–161·2]), and Rakai (125·1 [123·3–126·9]).

See Online for appendix

	Deaths	Person-years	Mortality per 1000 person-years (95% CI)	Age-standardised mortality per 1000 person-years (95% CI)
Not pregnant and more than 42 days post partum				
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 post partum				
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	4380	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)	..
Negative	710	266 578	2·7 (2·5–2·9)	..
Positive	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)	..

Data in the person-years column might not add exactly because of rounding.

Table 2: Mortality in pooled Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA) network data by pregnancy and HIV status, 1990–2012

	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%)

Data are n/N (%). Because of rounding, percentages do not always total 100%.

Table 3: Deaths in women and girls aged 15–49 years by study site, pregnancy, and HIV status

Mortality in HIV-uninfected women was 1.5 (95% CI 1.1–1.9) per 1000 person-years at uMkhanyakude, which was lower than that at the other sites combined (2.9 [0.27–0.31] per 1000 person-years).

Table 3 shows the distribution of deaths at each site classified by HIV status and whether or not women were pregnant or post partum. 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 3).

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 dataset was 10.6 (95% CI 10.4–10.9) per 1000 person-years. In HIV-infected women, overall mortality was 54.3 (52.4–56.3) per 1000 person-years compared with 2.7 (2.5–2.9) in HIV-uninfected women. It was 9.7 (9.4–10.1) per 1000 person-years in women of unknown HIV status, which was lower than the mean mortality of women with known HIV status (11.5 [11.2–11.9] per 1000 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 2 shows deaths, person-years of exposure, and resulting mortality by pregnancy or post-partum status and HIV status. 60 of 118 (50.8%) pregnant or post-partum women of known HIV status who died were

	Crude rate ratio (95% CI)		Population-attributable fraction	
	Pregnant or post partum	Not pregnant or post partum	Pregnant or post partum	Not pregnant or post partum
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
uMkhanyakude	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

Table 4: Crude rate ratio of mortality rates in HIV-infected and HIV-uninfected women and population-attributable fraction for HIV, by study site

infected with HIV (table 2). The appendix contains a further breakdown of these results by 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 post partum to that in HIV-uninfected women who were not pregnant or post partum was 20.5 (95% CI 18.9–22.4); in pregnant or post-partum women, the corresponding rate ratio is 8.2 (5.7–11.8; table 4). After adjustment for age, the rate ratio for women who were not pregnant or post partum fell to 19.0 (17.3–20.8) and that for pregnant or post-partum women increased slightly to 9.0 (6.1–13.1). Mortality rate ratios varied substantially across study sites (table 4). At all sites, the rate ratios were substantially higher in women who were not pregnant or post partum than in those who were pregnant or post partum, with the exception of Manicaland, where the ratios were very similar in the two groups (table 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 (appendix).

Figure 1 shows the mortality rates for women with known HIV status, broken down by availability of ART. Mortality fell substantially in HIV-infected women who

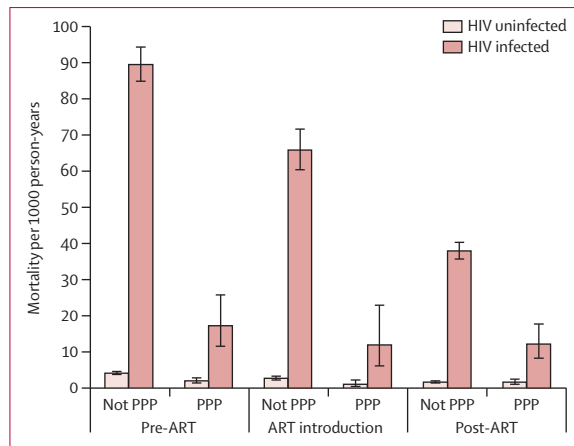


Figure 1: Mortality rates in HIV-infected and HIV-uninfected women, by pregnancy status and availability of ART

Pooled Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA) network data, 1990–2012. Bars are 95% CIs. ART=antiretroviral therapy. PPP=pregnant or post partum.

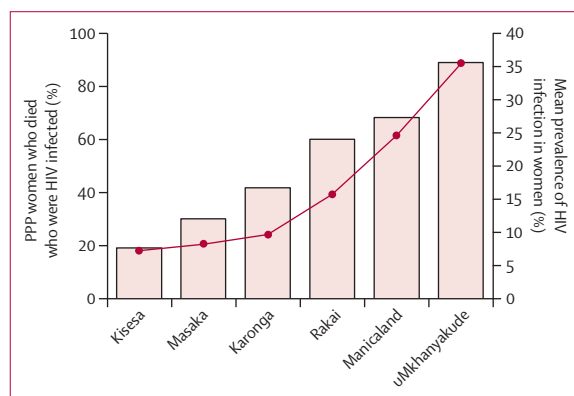


Figure 2: Proportion of pregnant or post-partum women infected with HIV at the time of their death of all deaths of pregnant or post-partum women with known HIV status, and mean prevalence of HIV infection in female population, by study site

Estimate of prevalence in the study population aged 15–50 years based on person-years lived with known HIV status. PPP=pregnant or post partum.

were not pregnant or post partum; 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 post partum, the fall was much smaller (0.70 [$p = 0.205$]).

In HIV-infected pregnant or post-partum women, the HIV-attributable rate of mortality was 11.8 per 1000 person-years (95% CI 8.4–15.3), and the HIV-attributable risk percentage was 87.7% (82.3–91.4). The corresponding HIV-attributable rate in HIV-infected women who were not pregnant or post partum was 51.8 per 1000 person-years (49.8–53.8) and the HIV-attributable risk percentage was 94.9% (94.4–95.3). In all pregnant or post-partum women with known HIV status, the population-attributable rate was 1.3 per 1000 person-years, and the PAF was 44.6%. For women with known HIV status who were not pregnant or post

partum, the population-attributable rate was 9.9 per 1000 person-years and the PAF was 77.6%.

Figure 2 compares, for each study, the proportion of pregnant or post-partum 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 post-partum women (range 7–35) was associated with that in pregnant or post-partum women who died (19–89). Prevalence of HIV infection in pregnant or post-partum women who died was between 2.5 and 4.5 times that in living women aged 15–50 years.

Discussion

In the pooled ALPHA data, HIV-infected pregnant or post-partum women had an eight-times higher risk of dying than did HIV-uninfected counterparts (panel). In women who were not pregnant or post partum, 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 post-partum women than that in HIV-infected women who were not pregnant or post partum. Thus, the HIV PAF is much smaller for pregnant or post-partum women than for women who were not pregnant or post partum (78%).

Lower excess mortality attributable to HIV in HIV-infected pregnant or post-partum women than in HIV-infected women who are not pregnant or post partum is perhaps not surprising. Although HIV has been classified by some analysts as an indirect cause of maternal death⁵—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.⁷ Excess mortality might be counter-balanced by the fact that fertility falls rapidly with duration of HIV infection³⁴ 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 post partum. 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.³⁵

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 guidelines³⁶ 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 post-partum 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 dataset 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, whereas the Joint UN Programme on HIV/AIDS (UNAIDS) estimate that the 2010 prevalence of HIV infection in pregnant women is 4·4% (unpublished).³⁷ The results of a systematic review¹³ showed that an estimated 25% of pregnancy-related deaths were attributable to HIV in sub-Saharan Africa. 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.³⁷ 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 post-partum 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%.^{4,38} However, confidential inquiries in South Africa suggest that roughly 70% of pregnant or post-partum women who die in hospital might be HIV infected,^{12,39} and estimates based on these data suggest a PAF for HIV of about 58%. In the pooled ALPHA dataset, 51% of the pregnant or post-partum 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—1015 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 per 100 000 in HIV-infected women and 500 per 100 000 in HIV-uninfected women)⁴ and the Institute for Health Metrics and Evaluation (490 per 100 000 in HIV-infected women and 170 per 100 000 in HIV-uninfected women).⁵ However, the ratios in the ALPHA dataset (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).¹² 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 6 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 dataset did not have an associated verbal autopsy, we might have missed some pregnancy-related deaths. 184 of 4892 (3·8%) deaths for which verbal

Panel: Research in context

Systematic review

To review the evidence on the proportion of maternal deaths attributable to HIV in Africa we relied on three sources. First, a systematic review⁷ of the causes of maternal deaths published in 2006 reported the proportion of maternal deaths in Africa attributable to HIV, but this review was based on only eight studies and methods to assign a death to HIV were not reported. Second, we searched PubMed, Embase, Popline, and African Index Medicus for studies comparing mortality during pregnancy and the post-partum period between HIV-infected and HIV-uninfected women.¹³ We identified 23 studies, which were published between 1991 and 2009. 17 were from sub-Saharan Africa, of which only two were population based.^{32,33} Third, we examined the modelled estimates published by the Institute for Health Metrics and Evaluation⁵ for 2011 and the Maternal Mortality Estimation Inter-agency Group⁴ for 2010. These models vary in their underlying assumptions, including those about whether deaths in HIV-infected pregnant or post-partum women should be classified as maternal, and results vary greatly.

Interpretation

Our study is, to our knowledge, the first to estimate the proportion of pregnancy-related or post-partum-related deaths attributable to HIV on the basis of empirical data from six community-based studies in eastern and southern Africa with HIV serological surveillance and verbal autopsies. HIV-infected pregnant or post-partum women have roughly eight times higher mortality than do their HIV-uninfected counterparts, and the excess mortality attributable to HIV in pregnant or post-partum women varies substantially depending on prevalence. Our findings emphasise the need to extend the focus of safe motherhood programmes beyond direct obstetric causes of death and call for a more rigorous assessment of HIV as a cause of pregnancy-related deaths.

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 (ie, 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.

Interstudy 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 uMkhanyukude to 5 years in Karonga, Kisesa, Masaka, and Rakai. The sensitivity analysis in the appendix shows that the effect of our assumptions on the mortality rate ratios of pregnant or post-partum 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 Centre⁴⁰) suggested that the overall mean prevalence of HIV infection might have been underestimated by as much as 30% in the pooled dataset—partly a result of the high prevalence in data from the Africa Centre, which also has the highest proportion of women with unknown HIV statuses. 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 post partum.

Our results show that, in populations with a high prevalence of HIV infection, a very high proportion of deaths during pregnancy or the post-partum 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.

Contributors

BZ, PB, TB, and CR conceived the study. BZ, CC, and CR wrote and revised the Article. BZ organised data collaboration, interpreted statistical analyses, and wrote and revised the Article. CC collated and checked multiple-site data, ran and interpreted statistical analyses, and wrote and revised the Article. MM collated and checked multiple-site data, wrote statistical programmes, and ran and interpreted statistical analyses. RI, JN-M, TL, AC, LR, and KH were responsible for data collection and preparation at the various study sites and commented on the Article. M-LN interpreted findings from the Africa Centre and helped with text revisions. JT organised data collaboration, interpreted statistical analyses, and helped with text revisions. PB commented on statistical analyses and text. TB commented on statistical analyses and helped with text revisions. CR interpreted statistical analyses.

Conflicts of interest

All authors received travel grants through the ALPHA Network to attend short workshops hosted at the study sites, at which they prepared and analysed the data and discussed the provisional results. We declare that we have no conflicts of interest.

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