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Direct maternal deaths attributable to HIV in the era of antiretroviral therapy: evidence from three population-based HIV cohorts with verbal autopsy

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Objective: To assess whether HIV is associated with an increased risk of mortality from direct maternal complications.

Design: Population-based cohort study using data from three demographic surveillance sites in Eastern and Southern Africa.

Methods: We use verbal autopsy data, with cause of death assigned using the InSilicoVA algorithm, to describe the association between HIV and direct maternal deaths amongst women aged 20–49 years. We report direct maternal mortality rates by HIV status, and crude and adjusted rate ratios comparing HIV-infected and uninfected women, by study site and by ART availability. We pool the study-specific rate ratios using random-effects meta-analysis.

Results: There was strong evidence that HIV increased the rate of direct maternal mortality across all the study sites in the period ART was widely available, with the rate ratios varying from 4.5 in Karonga, Malawi [95% confidence interval (CI) 1.6–12.6] to 5.2 in Kisesa, Tanzania (95% CI 1.7–16.1) and 5.9 in uMkhanyakude, South Africa (95% CI 2.3–15.2) after adjusting for sociodemographic confounders. Combining these adjusted results across the study sites, we estimated that HIV-infected women have 5.2 times the rate of direct maternal mortality compared with HIV-uninfected women (95% CI 2.9–9.5).

Conclusion: HIV-infected women face higher rates of mortality from direct maternal causes, which suggests that we need to improve access to quality maternity care for these women. These findings also have implications for the surveillance of HIV/AIDS-related mortality, as not all excess mortality attributable to HIV will be explicitly attributed to HIV/AIDS on the basis of a verbal autopsy interview.

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Keywords: Africa South of the Sahara, cause of death, HIV infections, maternal mortality, postpartum period, pregnancy

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Introduction

Early in the HIV epidemic, researchers noted the link between HIV and maternal mortality [1–3]. In Malawi, for example, the maternal mortality ratio tripled between 1980 and 1999, when the epidemic was growing [2]. Several studies have since documented that pregnant and postpartum women living with HIV have around eight times the risk of mortality compared with their uninfected counterparts; [4,5] however, the excess pregnancy-related mortality in women living with HIV (WLHIV) remains poorly understood.

HIV may increase the risk of mortality in pregnant and postpartum women through three main pathways. Firstly, some HIV-attributable deaths are likely caused by HIV/AIDS-related conditions, including pneumocystis pneumonia and tuberculosis. Pregnancy may accelerate HIV disease progression because of pregnancy-associated immunosuppression [6], although there is little epidemiological evidence to support this [7,8]. Secondly, HIV, or side effects of ART, may increase the risk or severity of complications of pregnancy, including sepsis, haemorrhage and hypertensive diseases of pregnancy. Finally, pregnant and postpartum WLHIV may have higher case-fatality associated with direct maternal causes as they are less likely to seek skilled assistance [9].

At the population level, the increased risk of direct maternal mortality amongst WLHIV may be offset by lower levels of fertility associated with HIV infection [10,11], but Byass *et al.* [12] found that mortality rates from direct maternal causes were four times higher among WLHIV than HIV-negative women. These estimates were based on pre-ART data in Eastern and Southern Africa. This articles provides a timely update, given the rapid expansion of ART, which has large mortality-inhibiting effects. The impact of ART on direct maternal mortality is not clear. ART may reduce the risk of some complications (e.g. sepsis) and increase the likelihood of women seeking skilled assistance by increasing contact with healthcare services or reducing stigma. However, it is likely to have no, or possibly an adverse, impact on other direct maternal complications. We explore the association between HIV and direct maternal causes of death amongst women, focusing on the period since ART became widely available.

Methods

Study sites

Three members of the network for Analysing Longitudinal Population-based HIV/AIDS data in Africa (ALPHA) contributed data for this analysis: [13] Karonga in Malawi, Kisesa in Tanzania and uMkhanyakude in South Africa. These partners completed multiple years of surveillance in their Demographic Surveillance Systems (DSS), conducted repeated population-based HIV serosurveys and, where a death was identified, administered a verbal autopsy interview in which a caregiver/relative of the deceased reports signs and symptoms preceding the death [14]. All three members have conducted at least 5 years of HIV serosurveys and over 80% of the deaths identified in the DSS can be linked to a verbal autopsy. Data were available from 2007 to 2012 in Karonga, 1994–2014 in Kisesa and 2004–2014 in uMkhanyakude. More details about the data collection procedures are given in the Supplementary Material, http://links.lww.com/QAD/B733 and the cohort profiles describing the respective DSS [15–17].

Data preparation

From each DSS, we extracted information on residency episodes, the events terminating residency episodes (death, out migration), HIV test dates and results and, for deaths, the signs and symptoms reported in a verbal autopsy.

The exposure of interest was person-time with and without HIV. HIV testing dates and results were linked to basic demographic (for example, age) and residency information, including DSS entry and exit dates, to provide the denominator population. Several assumptions were made when assigning person-time by HIV status. Time preceding the first HIV test was classified as unknown, as was person-time that occurred more than 5 years after the last HIV-negative test. Using a 5-year cut-off (as used by Byass *et al.* [12]) allowed for the estimation of mortality rates in HIV-negative individuals, but the exposure time was sufficiently short that increased mortality among seroconverters did not introduce bias. All person-time after an HIV-positive test result was treated as positive.

Person-time was additionally categorized by other key factors: education (none, some primary, some secondary and unknown); residence (urban, peri-urban and rural in Kisesa and uMkhanyakude, and by distance from a trading centre in Karonga); age; calendar period and whether ART was available (none, early ART or widely available). 'Early ART' is from when ART first became available at one government health facility and 'widely available' from when ART first became available at all local health facilities designated as ART providers under national guidelines [18]. Further details of these dates are provided in Supplementary Table 1, http://links.lww.com/QAD/B733. Kisesa was the only study site contributing data from the pre-ART era, and data for the early ART period were also available in uMkhanyakude. We restricted the analysis to women aged 20–49 years because of the differing fertility effects linked with HIV at younger ages.

Causes of death were ascertained from the signs and symptoms reported in the verbal autopsy using the

InSilicoVA tool (version 1.2.5 in R 3.5.1) [19]. InSilicoVA calculates a distribution of probabilities associated with each cause of death at the individual level and a distribution of counts of deaths for each cause at the population (or sub-population) level. We generated estimates for sub-populations defined by HIV status at time of death. Individual-level cause-specific probabilities of dying were then used to assign a cause of death for each individual. This was the cause of death with the highest probability. Where no cause had a probability greater than 0.4, the cause was assigned as indeterminate.

The outcome for this analysis was direct maternal deaths, defined by WHO as deaths during pregnancy or up to 42 days postpartum resulting from 'obstetric complications of the pregnancy state (pregnancy, labour and the puerperium), from interventions, omissions, incorrect treatment or from a chain of events resulting from any of the above' [20]. The cause categories from InSilicoVA that most closely correspond to this definition, and were therefore combined to give the outcome, are: ectopic pregnancy, abortion-related death, pregnancy-induced hypertension, obstetric haemorrhage (including ruptured uterus), obstructed labour, pregnancy-related sepsis, and anaemia of pregnancy. The ICD-10 equivalent codes for each of these categories is provided in Supplementary Table 2, http://links.lww.com/QAD/B733. The key question in the verbal autopsy tool to identify pregnancy-related deaths asks whether any woman who died was pregnant or within 42 days of delivery, but we cannot rule out that some women who died beyond 42 days postpartum would be classified as a direct maternal death through the algorithm. A further category 'other/unspecified maternal causes' was not included in our outcome as it includes indirect maternal causes of death 'from previous existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by physiologic effects of pregnancy' [20]. For a sensitivity analysis, we also used a more restrictive definition of direct maternal causes excluding anaemia, as risk of anaemia is elevated with HIV.

Statistical methods

We calculated the number of deaths in the DSS that received a verbal autopsy, and the percentage of deaths attributed to direct maternal deaths, stratified by HIV status. InSilicoVA generated cause-specific mortality fractions for each sub-population (HIV status). The methods to produce these estimates are described in detail elsewhere [19].

Using survival analysis, the total person-years of observation, numbers of direct maternal deaths and direct maternal mortality rates were estimated by HIV status. Rate ratios, comparing direct maternal mortality rates in WLHIV with those of HIV-negative women were calculated using Poisson regression and were adjusted for age, calendar period, residence and education. These analyses were stratified by ART availability, with cross-site comparisons based on results from the period when ART was widely available. This analysis was conducted first using all direct maternal deaths, and then using the more restricted definition excluding anaemia. Person-years of women who died but who did not receive a verbal autopsy, were dropped from these analyses; however, we undertook a sensitivity analysis assuming all HIV-negative deaths missing a verbal autopsy were direct maternal deaths, and no HIV-positive deaths were direct maternal. This sensitivity analysis provides the most conservative estimates of the association between HIV and direct maternal mortality. For the Karonga DSS, we were also able to evaluate the sensitivity of our results to the cause of death attribution method as it is the only of the three DSS that routinely interprets verbal autopsies using physician review. In physician review, the signs and symptoms reported in the verbal autopsy, and the narrative description by the respondent of the events leading up to the death are reviewed independently by two physicians who assign a cause of death; discrepancies between the two physicians are moderated by a third physician, who assigns the final cause of death.

Pooled estimates of the association between HIV and direct maternal mortality were calculated, combining the adjusted rate ratios for the period since ART was widely available from the three study sites. Estimates were pooled using the DerSimonian and Laird method for random effects meta-analysis. Evidence for between-study was assessed using I^2 and the P-value from the test of heterogeneity.

Ethics and consent

Ethical approval for this analysis was granted by the London School of Hygiene and Tropical Medicine ethics committee (ref: 6522). Written informed consent was provided by study participants (which is the family member/caregiver of the deceased in the case of the verbal autopsy) for the anonymized analysis of their data.

Results

Women aged 20–49 years contributed 235 291 person-years of follow-up for this analysis across the three study sites. In Karonga, there were 35 426 years of follow-up, all of which fell in the ART widely available period. For Kisesa, there were 77 408 person-years of follow-up: 31 112 in the ART widely available phase, 15 248 in the early ART period and 31 048 before ART was available. In uMkhanyakude, there were 96 647 persons-years of follow-up when ART was widely available and 25 810 years in the early ART period, giving 122 457 person-years overall.

A total of 2186 verbal autopsies among women 20–49 could be assigned a cause of death. In Karonga, all deaths identified in the DSS received a verbal autopsy ($N = 158$). In Kisesa, 80.9% of the 570 deaths received a verbal autopsy ($N = 461$) and in uMkhanyakude 96.4% of 1625 deaths did ($N = 1567$). Table 1 describes verbal autopsy coverage and the number of verbal autopsies by key characteristics of the population. The percentage of verbal autopsies with known HIV status was 58% in Karonga, 59% in Kisesa and 65% in uMkhanyakude. When restricting analyses to the period in which ART is widely available, we had 1346 verbal autopsies, with uMkhanyakude contributing the most ($N = 1065$) and Kisesa the least ($N = 123$).

The percentage of deaths attributed to direct maternal causes amongst women 20–49 years varied between sites; when ART was widely available, the percentages were 6.2% in uMkhanyakude, 12.7% in Karonga, and 18.3% in Kisesa. The percentage of deaths attributed to direct maternal causes was consistently higher amongst HIV-negative women compared with WLHIV (Supplementary Figure 1, http://links.lww.com/QAD/B733). Combining data for all periods, specific causes of direct maternal deaths varied by HIV status between the sites but there was no statistical evidence for differences in the causes between WLHIV and HIV-negative women (Supplementary Figure 2, http://links.lww.com/QAD/B733). Amongst HIV-negative women, the most common cause was obstetric haemorrhage in Karonga and uMkhanyakude (12.5% and 3.6%, respectively), and pregnancy-related sepsis in Kisesa (10.3%). For WLHIV, the most common cause of direct maternal deaths was obstetric haemorrhage in Karonga (3.9%), ectopic pregnancy in Kisesa (3.7%) and anaemia of pregnancy in uMkhanyakude (3.7%).

When ART was widely available, the direct maternal mortality rate was 59.0 per 100 000 person-years in uMkhanyakude [95% confidence Interval (CI): 45.5–76.5], 79.0 in Karonga (95% CI: 54.6–114.5) and 80.4 in Kisesa (95% CI: 54.3–118.9). Figure 1 and Supplementary Table 3, http://links.lww.com/QAD/B733 shows these direct maternal mortality rates per 100 000 person-years, by age group and HIV status. Direct maternal mortality is generally higher among WLHIV, albeit with large confidence bounds for some ages. Estimates of direct maternal mortality rates in the pre-ART and early ART period are provided in Supplementary Figure 3, http://links.lww.com/QAD/B733. Mortality rates attributable to non direct maternal causes of deaths are presented in the Supplementary Materials, http://links.lww.com/QAD/B733.

In all study sites, there was evidence that direct maternal mortality was higher amongst WLHIV after adjusting for age, calendar period, residence and education (Table 2) when ART was widely available. The magnitude of the

Table 1. Number of deaths identified through the demographic surveillance system, and the number and percentage of these deaths that received a verbal autopsy, by antiretroviral therapy availability, study site and key characteristics of the population.

	Karonga				Kisesa				uMkhanyakude			
	Widely available		None		Early ART		Widely available		Early ART		Widely available	
	Deaths in DSS *N*	Deaths with verbal autopsy *N* (%)	Deaths in DSS *N*	Deaths with verbal autopsy *N* (%)	Deaths in DSS *N*	Deaths with verbal autopsy *N* (%)	Deaths in DSS *N*	Deaths with verbal autopsy *N* (%)	Deaths in DSS *N*	Deaths with verbal autopsy *N* (%)	Deaths in DSS *N*	Deaths with verbal autopsy *N* (%)
Overall	158	158 (100)	316	245 (77.5)	108	93 (86.1)	146	123 (84.2)	516	502 (97.3)	1109	1065 (96.0)
Age												
20–29	39	39 (100)	114	92 (80.7)	34	29 (85.3)	39	31 (79.5)	158	154 (97.5)	362	345 (95.3)
30–39	65	65 (100)	128	94 (73.4)	43	39 (90.7)	58	51 (87.9)	216	210 (97.2)	446	428 (96.0)
40–49	54	54 (100)	74	59 (79.7)	31	25 (80.6)	49	41 (83.7)	142	138 (97.2)	301	292 (97.0)
Education												
None	2	2 (100)	50	41 (82.0)	12	11 (91.7)	14	12 (85.7)	48	47 (97.9)	40	39 (97.5)
Some primary	115	115 (100)	143	120 (83.9)	78	65 (83.3)	75	67 (89.3)	194	189 (97.4)	303	294 (97.0)
Some secondary	36	36 (100)	7	5 (71.4)	4	4 (100.0)	7	6 (85.7)	216	213 (98.6)	568	547 (96.3)
Tertiary	–	–	–	–	–	–	–	–	33	32 (97.0)	173	163 (94.2)
Unknown	5	5 (100)	116	79 (68.1)	14	13 (92.9)	50	38 (76.0)	25	21 (84.0)	25	22 (88.0)
HIV status												
Negative	33	33 (100)	72	61 (84.7)	35	29 (82.9)	30	28 (93.3)	17	17 (100.0)	74	71 (95.9)
Positive	59	59 (100)	98	80 (81.6)	35	32 (91.4)	46	42 (91.3)	209	209 (100.0)	722	722 (100.0)
Unknown	66	66 (100)	146	104 (71.2)	38	32 (84.2)	70	53 (75.7)	283	270 (95.4)	289	251 (86.9)

ART, antiretroviral therapy.

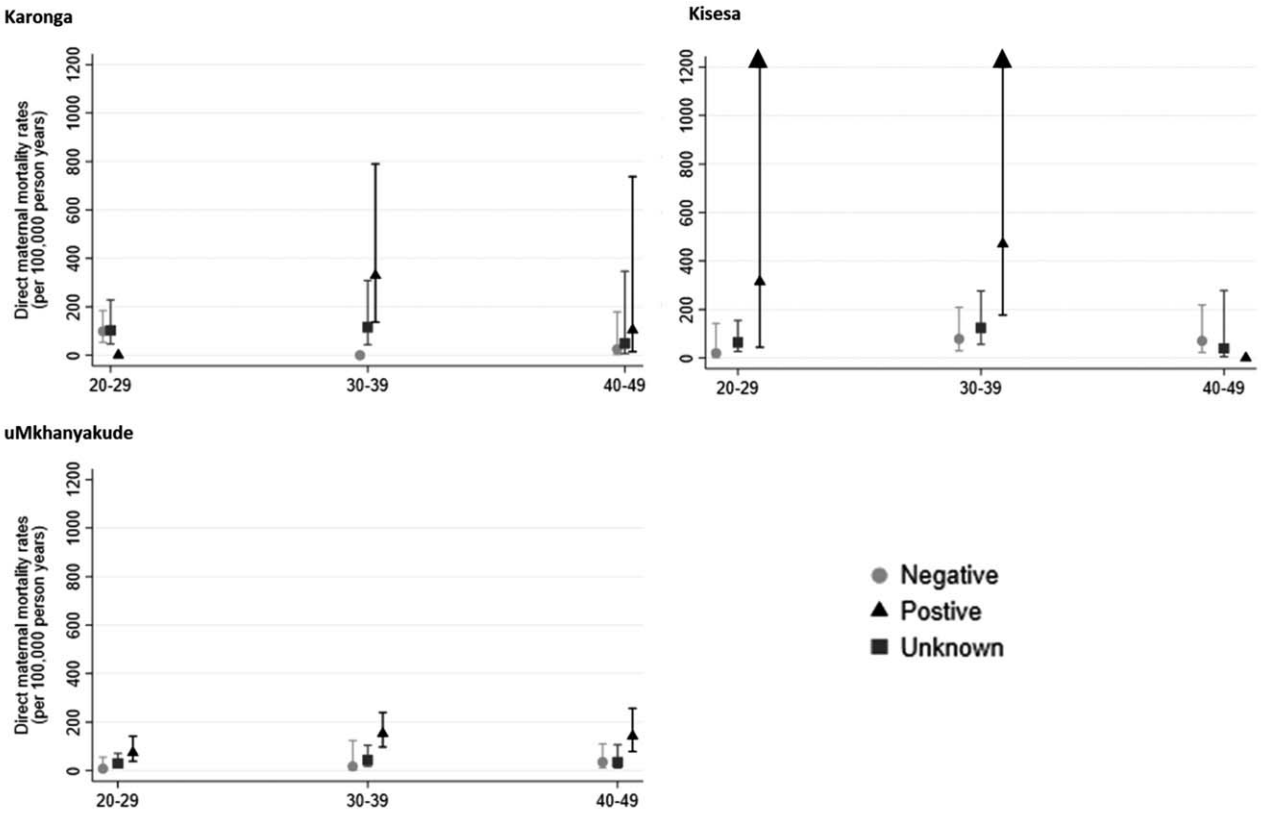

Fig. 1. Direct maternal mortality rates per 100 000 person-years by HIV status and age group in the period since ART became widely available, for each study site. Cause of death assigned using InSilicoVA tool.

higher rate of direct maternal mortality varied from 4.52 times in WLHIV in Karonga (95% CI: 1.62–12.63) to 5.92 in uMkhanyakude (95% CI: 2.30–15.21). Analysis of earlier periods was only possible for Kisesa; there was little evidence for a change in the rate ratio by ART availability – when ART was not available, the rate ratio was 4.36 (95% CI: 1.19–15.98) and in the early ART phase, it was 4.91 (95% CI: 1.49–16.19). Only a single direct maternal death was identified amongst HIV-negative women in uMkhanyakude in the early ART phase, negating the calculation of an adjusted rate ratio. Removing anaemia of pregnancy did not change the results when ART was widely available for Kisesa, but it slightly reduced the rate ratio in Karonga (from 4.52 to 4.44) and substantially reduced it in uMkhanyakude from 5.92 to 1.39 (95% CI: 0.44–4.34, P-value = 0.4) (Supplementary Table 4, http://links.lww.com/QAD/B733).

Sensitivity analyses were undertaken in Kisesa and uMkhanyakude, classifying HIV-negative deaths that did not have a verbal autopsy completed as direct maternal (Kisesa: two deaths with four person-years of follow-up, uMkhanyakude: three deaths with 13 person-years of follow-up) and HIV positive deaths without a verbal autopsy as non obstetric (Kisesa: four deaths and four person-years of follow-up). Although the association between HIV and direct maternal mortality was attenuated, there was still evidence for an association (Supplementary Table 5, http://links.lww.com/QAD/B733). In Karonga, there was a decrease in the adjusted rate ratio when using physician review rather than InSilicoVA to ascertain the cause of death, with the rate ratio of direct maternal mortality in WLHIV compared with their uninfected counterparts dropping from 4.23 to 3.31 (95% CI: 1.14–9.58) (Supplementary Table 6, http://links.lww.com/QAD/B733).

The individual study and pooled estimates of the association between HIV and direct maternal mortality are given in Fig. 2. On the basis of data from the three studies, we estimated that WLHIV have 5.23 times the rate of direct maternal deaths than HIV-negative women (95% CI: 2.89–9.45). There was no evidence of between-study heterogeneity ($I^2 = 0\%$, P-value = 0.93).

Discussion

Pooled estimates from the three study sites when ART was widely available indicate that WLHIV aged 20–49 years have over five times the rate of direct maternal mortality compared with their uninfected counterparts, after

Table 2. Direct maternal mortality rates and rate ratios for direct maternal mortality by HIV status, study and antiretroviral therapy availability, in women aged 20–49.

	Number of direct maternal deaths	Person years	Rate per 100 000	Crude rate ratio	Crude *P*-value	Age-adjusted rate ratio	Age-adjusted *P*-value	Adjusted rate ratio[a]	Adjusted *P*-value[b]
ART widely available									
Karonga									
Negative	11	20 829	53 (29–95)	1		1		1	
Positive	6	3229	186 (83–414)	3.52 (1.30–9.52)		4.10 (1.48–11.35)		4.52 (1.62–12.63)	
Unknown	11	11 367	97 (54–175)	1.83 (0.79–4.23)	0.05	1.80 (0.78–4.16)	0.03	2.02 (0.79–5.13)	0.02
Kisesa									
Negative	8	14 322	56 (28–112)	1		1		1	
Positive	5	1615	310 (129–744)	5.54 (1.81–16.94)		4.85 (1.57–14.93)		5.21 (1.68–16.12)	
Unknown	12	15 174	79 (45–139)	1.42 (0.58–3.46)	0.03	1.46 (0.59–3.61)	0.04	1.67 (0.67–4.17)	0.03
uMkhanyakude									
Negative	5	27 031	18 (8–44)	1		1		1	
Positive	39	32 402	120 (88–165)	6.51 (2.56–16.51)		6.12 (2.40–15.60)		5.92 (2.30–15.21)	
Unknown	13	37 214	35 (20–60)	1.89 (0.67–5.30)	<0.001	1.86 (0.66–5.23)	<0.001	1.94 (0.68–5.50)	<0.001
Early ART									
Kisesa									
Negative	9	8956	100 (52–193)	1		1		1	
Positive	4	682	587 (220–1564)	5.84 (1.80–18.97)		5.37 (1.65–17.54)		4.91 (1.49–16.19)	
Unknown	9	5610	160 (83–308)	1.60 (0.63–4.02)	0.04	1.60 (0.63–4.09)	0.05	1.59 (0.62–4.10)	0.06
uMkhanyakude[b]									
Negative	1	7107	14 (2–100)	1		-		-	
Positive	4	4109	97 (37–259)	6.92 (0.77–61.90)		-		-	
Unknown	14	14 595	96 (57–162)	6.82 (0.90–51.84)	0.04	-	-	-	-
ART not available									
Kisesa									
Negative	11	17 133	64 (36–116)	1		1		1	
Positive	3	1163	258 (83–800)	4.02 (1.12–14.40)		4.06 (1.13–14.59)		4.36 (1.19–15.98)	
Unknown	9	12 751	71 (37–136)	1.10 (0.46–2.65)	0.18	1.18 (0.49–2.87)	0.18	1.27 (0.51–3.14)	0.16

ART, antiretroviral therapy.
[a]Adjusted for age group, calendar period, residence and education level in Karonga and uMkhanyakude. In Kisesa, estimates are adjusted for age group, calendar period and residence.
[b]Adjusted rate ratios were not calculated due to small numbers, notably amongst the HIV-negative group.

accounting for confounders including age and education. This elevated risk of mortality from direct maternal complications will account for a large percentage of the excess mortality attributable to HIV in pregnant and postpartum women identified in previous studies [4,5].

There was considerable variation between the study populations in the percentage of deaths to women attributed to direct maternal causes, from 6.2% in uMkhanyakude to 18.3% in Kisesa. In all three study sites, however, the percentages were higher than national-level estimates from the 2016 Global Burden of Disease (uMkhanyakude 6.2% versus South Africa 1.2%; Karonga 12.7% versus Malawi 5.8%; Kisesa 18.3% versus 12.4% Tanzania) [21]. Due to the rural location of the study sites and the basic level of healthcare available, this is not surprising. Between-study differences were also observed in rates of direct maternal mortality, with direct maternal mortality rates lower in uMkhanyakude compared with the other study sites. This is partly explained by the lower

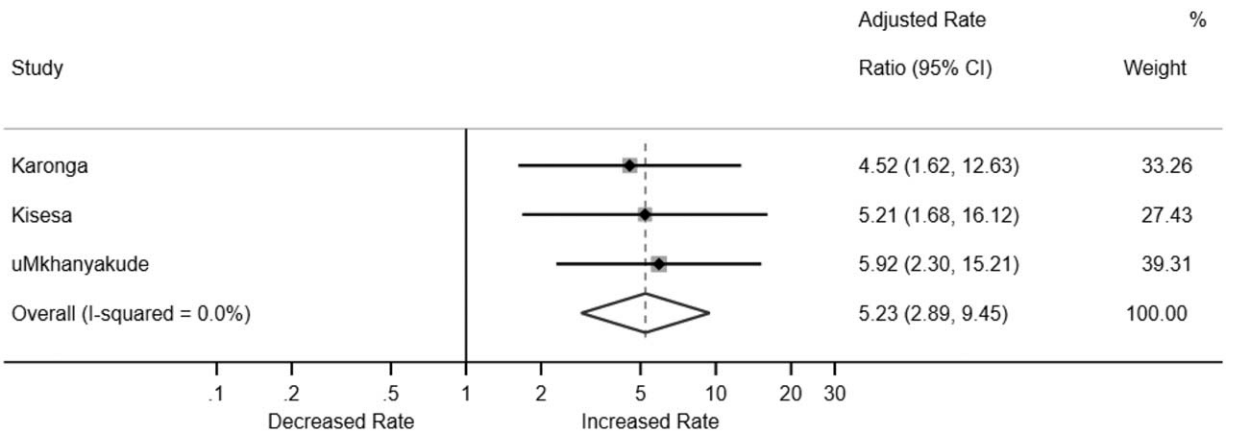

Fig. 2. Association of HIV and direct maternal mortality since ART became widely available, for each of the study sites and the pooled estimate calculated from random-effects meta-analysis.

levels of fertility in South Africa [22]. Another important factor is healthcare systems, with many more births occurring in health facilities with skilled birth attendants in South Africa, compared with Malawi and Tanzania [23].

Exploring specific causes of direct maternal deaths is limited by the small number of deaths in each study site, and the challenges of assigning specific causes of death using verbal autopsy. There are, however, a number of biological pathways that may explain the elevated mortality from direct maternal complications in WLHIV. Immune suppression associated with HIV is likely to leave WLHIV more vulnerable to pregnancy-related sepsis [24,25]. Studies have also documented an increased risk of pregnancy-related anaemia in WLHIV in sub-Saharan Africa [26,27], but the cause behind this is complex: causes of anaemia include blood loss and ineffective red blood cell production because of deficiencies in iron, which are independently linked both to HIV and pregnancy [28]. Co-infection with malaria, which is more common and more severe amongst pregnant WLHIV [29], likely plays a role in increasing anaemia, particularly in Kisesa where malaria is a leading cause of death [16]. Blood loss during delivery may be more severe for WLHIV because of HIV-related thrombocytopenia; lower platelet counts in the blood can lead to problems in coagulation causing higher levels of mortality because of haemorrhage and anaemia. There are very few epidemiological studies looking at the link between HIV and thrombocytopenia in pregnant women, and these yield conflicting results [30,31].

Poor access to, and quality of, healthcare may also increase the risk of mortality from obstetric complications in WLHIV. Studies have generally shown similar or better engagement with ANC amongst WLHIV compared with HIV-negative women in sub-Saharan Africa [32,33]. The evidence linking HIV and poor-quality maternity care is scant. In studies conducted in four maternity hospitals in Kisumu (Kenya) and one large referral hospital in Dar es Salaam (Tanzania), healthcare workers reported that they were trained to treat WLHIV in the same way as HIV-negative women [34,35]. However, in the Kenyan study, several providers reported that knowing a woman is HIV-positive would lead them to handle a woman with 'extra care', and in both settings, providers mentioned that WLHIV may have not have received the same care as HIV-negative women in the past [34,35]. A study describing the prevalence of disrespect and abuse during labour and delivery in 40 facilities across Malawi found that, through observation of over 2000 deliveries, WLHIV were less likely to be asked about their preferred delivery position or other problems she might be concerned about [36].

There are a number of limitations that need to be considered when interpreting the results. Firstly, it is well recognized that verbal autopsies are imprecise, and cause of death misclassifications are inevitable. We may have overestimated the association between HIV and direct maternal mortality if HIV/AIDS-related deaths have similar symptom patterns as some direct maternal deaths. This is possible for deaths that were attributable to anaemia and ectopic pregnancy but unlikely for most other direct maternal causes that have relatively distinctive symptom patterns. Removing anaemia of pregnancy from our definition of direct maternal deaths did not change our conclusions in Karonga and Kisesa but led to a drop in the rate ratio for uMkhanyakude such that there was no longer evidence of a difference in direct maternal mortality in WLHIV and HIV-negative women. Secondly, there are limitations in using algorithms to assign cause of death using verbal autopsy data. Critically, they do not use information from the narrative section of the verbal autopsy where the respondent gives their own account of the events leading up to the death. Finally, some of the association we observe may be because of residual confounding. For example, whilst we adjusted for education and area of residence, this may not be sufficient to account for socioeconomic differences between WLHIV and HIV-negative women that may lead to differences in risk of mortality from direct maternal complications. We also lacked data on other infections. Other STIs, for example, are more likely to occur in WLHIV and may leave women at increased risk of complications [37].

We considered direct maternal mortality rates amongst women of reproductive age, rather than focussing on just the subset of pregnant and postpartum women because of data availability. Notably, we lacked comprehensive data on dates of pregnancy and pregnancies that did not result in a livebirth across some of the study sites. HIV lowers fertility in the age groups under consideration, therefore our estimates of the rate ratio comparing obstetric mortality in WLHIV and HIV-negative women will be lower than if we had calculated the rate ratio amongst only women who became pregnant. However, we expect that the rate ratio is unlikely to be much larger for women who become pregnant. Previous studies utilizing DHS [11] or data from the same study sites [10,38] show that, with ART, the gap in fertility rates between HIV-positive and negative women is narrowing slightly compared with the pre-ART era; however, some differences in fertility remain.

We find consistent evidence across the study sites suggesting HIV increases the risk of direct maternal mortality. This has implications for the measurement of HIV/AIDS mortality, as well as for service provision for pregnant and postpartum WLHIV. When measuring the impact of HIV/AIDS on mortality using verbal autopsy data, it is insufficient to rely on the number of deaths that are directly classified as HIV/AIDS. Measurement should account for the percentage of deaths that are attributable to HIV but not explicitly classified as such. These results also suggest we are failing to deliver quality maternity

services to WLHIV, who are at elevated risk of this largely preventable cause of mortality. Understanding the relative importance of the pathways that leave WLHIV at increased risk of direct maternal mortality (e.g. biological increase in risk of anaemia/sepsis, and healthcare system or behavioural barriers to receiving quality care) would be useful. WLHIV may need closer monitoring for complications, such as sepsis, and barriers that WLHIV face barriers in accessing quality antenatal, delivery and postnatal care should be addressed.

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Conflicts of interest

There are no conflicts of interest.

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