High Proportion of Deaths Attributable to HIV Among Postpartum Women in Botswana Despite Widespread Uptake of Antiretroviral Therapy

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Abstract

Mortality in the postpartum period may be impacted by antiretroviral therapy (ART) received in pregnancy, and whether ART is continued in the postpartum period. HIV-infected and HIV-uninfected mothers were enrolled within 48 h of delivery at five public hospital maternity wards throughout Botswana and followed for 24 months. Maternal deaths were reported by one of the approved contacts given by the mother at enrollment. Detailed information on the cause of death was not available. Risk factors for 24-month mortality were assessed using Cox proportional hazard models. From February 2012 to March 2013, 3000 mothers (1499 HIV infected and 1501 HIV uninfected) were enrolled, and 2985 (99.5%) were followed to 24 months or death, or until the death of their child. There were 26 total maternal deaths through 24 months postpartum [439 per 100,000 person-years (p-y)], 22 among HIV-infected women (758 per 100,000 p-y) and 4 among HIV-uninfected women (132 per 100,000 p-y). Maternal HIV-infection (aHR 5.0, 95% CI 1.6–15.2) and infant birth injury (aHR 3.8, 95% CI 1.3–11.4) were independent risk factors for maternal death. Universal ART in pregnancy became the standard-of-care after June 2012, and 978 (65%) women received ART in pregnancy; by 24 months postpartum or end of follow-up, 1148 (79%) had started ART overall. There was no significant difference in 24-month mortality among HIV-infected women who took ART in pregnancy and continued throughout the follow-up period compared with HIV-infected women who took ART or zidovudine in pregnancy and stopped postpartum (aHR 0.6, 95% CI 0.2–1.7). Despite high uptake of ART in pregnancy and postpartum, women with HIV infection in Botswana are five times more likely to die than HIV-uninfected women in the 24 months postpartum.

Keywords: HIV, prenatal, antiretroviral

Introduction

REDUCING MATERNAL mortality remains a top public health priority, particularly in sub-Saharan Africa where >60% of maternal deaths occur.¹ HIV infection disproportionately impacts women of reproductive age, increasing the risk of mortality as much as 20 times that of HIV-uninfected women.² HIV infection also increases the risk of mortality

during pregnancy and early postpartum (<42 days from delivery) with a maternal mortality rate ratio of 8.2 in a pooled analysis of studies from Africa.³ Isolating the effect of the HIV epidemic on late maternal mortality (up to 12 months postpartum) in sub-Saharan Africa is challenging due to difficulties classifying cause of death in this setting and defining whether mortality is related to complications during pregnancy and delivery or to ongoing HIV infection.^{4,5} Most

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studies of postpartum mortality among HIV-infected women were performed before widespread use of antiretroviral therapy (ART) for prevention of mother to child transmission (PMTCT) and for maternal treatment, both of which would be expected to improve maternal outcomes.⁵⁻⁷

Our aims were to determine the impact of HIV infection on 24-month postpartum mortality and evaluate risk factors for mortality among HIV-infected women in a setting with widespread uptake of ART and PMTCT services. We prospectively followed both HIV-infected and HIV-uninfected women in Botswana and ascertained maternal vital status at 24 months postpartum.

Materials and Methods

We enrolled women within 48 h of delivery at five public hospital maternity wards throughout Botswana: one large tertiary referral center, one midsize district hospital, and three smaller regional hospitals. We approached equal numbers of HIV-infected and HIV-uninfected women daily to keep accrual similar throughout the study period. Exclusion criteria included living >100 km from the hospital, being unwilling to be contacted by telephone, or not providing a contact number (women without their own phones were encouraged to provide a number for a relative, friend, neighbor, or workplace). After the study enrollment visit, follow-up contacts were conducted by phone at 1 month, 3 months, and then every 3 months until 24 months postpartum. With permission, participants who could not be contacted by phone were traced to their home where a visit was performed in person. Maternal demographics, medical and obstetric history, and HIV testing and treatment history were collected at study enrollment. During follow-up contacts, we collected information on child feeding practices, HIV testing (for HIV uninfected), ART treatment (for HIV infected), and child mortality. Mothers were followed until death, completion of study, or death of their child. Information about the maternal death was collected from one of the approved contacts given by the mother at enrollment, typically a family member or neighbor. Child mortality during the 24-month follow-up period has been previously described.⁸

During the study, HIV-infected women received ART and PMTCT services in the government system according to Botswana national HIV guidelines. From February to May 2012, Botswana followed WHO Option A for PMTCT. All HIV-infected pregnant women (and all HIV-infected adults) with $CD4 \leq 350$ cells/mm³ or WHO clinical stage 3 or 4 were eligible for lifelong combination ART; if $CD4 \leq 250$ cells/mm³, zidovudine (ZDV)/lamivudine (3TC)/nevirapine (NVP) was prescribed or if $CD4 > 250$ cells/mm³, ZDV/3TC/Lopinavir/ritonavir (LPV/r) was prescribed. Pregnant women with $CD4$ counts >350 cells/mm³ were eligible to start ZDV alone during pregnancy (stopped at 6 weeks postpartum). Starting in June 2012, the first-line ART regimen for all adults was changed to TDF/FTC/EFV (Atripla) and Botswana switched to WHO Option B for PMTCT. All pregnant women, regardless of $CD4$ count, were eligible to receive Atripla and pregnant women with $CD4 > 350$ stopped ART after the mother to child transmission (MTCT) risk period (postpartum if the woman chose not to breastfeed, or after weaning). WHO Option B+, initiating ART in all pregnant women and continuing life-long, was not implemented in

Botswana until after the study period (2016). For citizens of Botswana, the Botswana government provides free healthcare, including free HIV testing and ART.

Statistical analysis

The crude mortality rate is presented as deaths per 100,000 person-years (p-y) of follow-up. We do not present a maternal mortality ratio because no deaths in pregnancy or childbirth are included. Risk factors for mortality were assessed using Cox proportional hazards model, including all participants, both HIV infected and HIV uninfected. The effect of maternal $CD4$ count and PMTCT strategy on mortality was assessed in a separate Cox proportional hazard model, including only HIV-infected women. The first $CD4$ count drawn in pregnancy was used in all analyses. PMTCT strategy was categorized as (1) women who received ART in pregnancy and throughout the 24-month postpartum period, (2) women who received ZDV or ART during pregnancy, but this was stopped in the immediate postpartum period, and (3) women who received no ART during pregnancy. Given the limited number of maternal deaths, covariates to include in the adjusted model assessing the effect of HIV status on mortality were chosen *a priori* based on review of maternal mortality literature and were included in the final model if the covariate had a *p* value <0.10 in univariate analysis and not colinear with HIV-infection status.

Ethical approval

Ethical approval for this study was granted by the Human Research Development Committee in Botswana and Institutional Review Board at the Harvard T.H. Chan School of Public Health. Written informed consent was obtained from each participant before enrollment. Permission to perform home visits was asked separately, and participants who refused home visits were not excluded from the study.

Results

We enrolled 3000 women between February 2012 and March 2013, 1499 HIV infected and 1501 HIV uninfected. Study enrollment characteristics are shown in Table 1.

We had complete follow-up to either 24 months postpartum or death for 2879 (96%); 106 (3.5%) were not followed after death of their child; 9 (0.3%) withdrew from the study; and 6 (0.2%) were lost to follow-up. Among the 106 women not followed after the death of their child, 82 (77%) were HIV infected (reflecting the higher child mortality among HIV-exposed children),⁸ otherwise there was no significant differences among women with and without complete follow-up. The proportion of women completing each follow-up contact ranged from 87.2% (6 month follow-up) to 99.8% (24 month follow-up). Home visits were performed in $<1\%$ of overall follow-up contacts. Among HIV-infected women, 976 (65%) received ART in pregnancy, 408 (27%) received ZDV alone, 111 (7%) received no antiretroviral medication (ARVs), and ARV use was not known for 4 (0.3%). There were 26 total maternal deaths in the 24 months postpartum (439 per 100,000 p-y), 22 among HIV-infected women (758 per 100,000 p-y) and 4 among HIV-uninfected women (132 per 100,000 p-y). One death occurred in the first 42 days (HIV-infected woman), 14 (54%) deaths occurred between 42 days and 12 months,

TABLE 1. MATERNAL, PREGNANCY, DELIVERY, AND BIRTH OUTCOME CHARACTERISTICS AT STUDY ENROLMENT, BY HIV STATUS, AMONG 3000 WOMEN IN BOTSWANA

<i>Baseline characteristics</i>	<i>HIV-infected mothers (N=1499), n (%)</i>	<i>HIV-uninfected mothers (N=1501), n (%)</i>
Maternal sociodemographic characteristics		
Age, median [range]	29 [18–47]	24 [18–47]
Married	122 (8)	145 (10)
No or primary education	197 (13)	77 (5)
Primary water source		
Piped into house	209 (14)	317 (21)
Tap in the yard	977 (65)	1007 (67)
Communal standpipe	301 (20)	170 (11)
Toileting facilities		
Indoor toilet	289 (19)	434 (29)
Private latrine for compound	1028 (69)	946 (63)
Shared latrine with other compounds	69 (5)	53 (4)
No latrine facility	107 (7)	60 (4)
Electricity in the home	799 (53)	987 (66)
Housing type		
Formal: tin roof, concrete	1011 (67)	1057 (70)
Informal: mud roof or thatched	112 (7)	69 (5)
Mixed formal/informal ^a	374 (25)	375 (25)
No stable housing	2 (0.1)	0 (0)
Medical and pregnancy characteristics		
Primigravid	244 (16)	675 (45)
Gravidity ≥4	545 (36)	199 (13)
Any reported pregnancy risk factor ^b	168 (12)	200 (13)
Any hospitalization during pregnancy	205 (14)	192 (13)
Any antihypertensive therapy during pregnancy	125 (8)	100 (7)
Rh factor negative	41 (3)	49 (3)
Delivery method and birth outcome		
Delivery method		
Vaginal	1334 (88)	1387 (91)
Elective Cesarean section	21 (1)	16 (1)
Emergency Cesarean section	160 (11)	115 (8)
Birth outcome		
Preterm (<37 weeks)	277 (18)	182 (13)
Low birth weight (<2500 g)	254 (17)	113 (7)
Infant birth injury ^c	67 (4)	110 (7.3)

The data in this table are presented as *N* (%) unless otherwise specified.

^aFormal housing defined as having tin roof and concrete walls, informal housing defined as mud walls and thatched roof, and Mixed formal/informal housing defined as having attributes of both formal and informal housing.

^bAny pregnancy risk factor includes smoking, alcohol use, height <1.5 m, and/or presentation for antenatal care in the third trimester.

^cInfant birth injuries included caput (85%), cord around the neck (9%), hematoma (2%), and other (4%).

FIG. 1. Maternal deaths over time by HIV-infection status.

TABLE 2. RISK FACTORS FOR MATERNAL DEATH UP TO 24 MONTHS POSTPARTUM AMONG 3000 WOMEN IN BOTSWANA

Selected risk factors for mortality	All mothers (N=3000)		HIV-infected mothers (N=1499)	
	Univariate HR (95% CI)	Adjusted HR (95% CI) ^a	Univariate HR (95% CI)	Adjusted HR (95% CI) ^b
HIV infection	5.7 (2.0–16.6)	5.0 (1.6–15.2)	—	—
Infant birth injuries	2.9 (1.0–8.5)	3.8 (1.3–11.4)	3.5 (1.0–11.9)	6.9 (1.9–25.3)
Maternal age	1.1 (1.0–1.1)	1.0 (0.96–1.1)	1.0 (0.9–1.1)	—
No latrine available in compound	4.5 (1.4–13.8)	1.2 (0.9–1.8)	3.3 (1.0–10.9)	1.3 (0.7–2.4)
Housing mixed formal/informal	2.0 (0.9–4.5)	1.3 (0.9–2.0)	2.8 (1.2–6.7)	1.3 (0.7–2.3)
Rh factor negative	1.6 (1.0–2.6)	1.5 (0.9–2.4)	1.7 (1.0–2.7)	1.7 (0.9–3.3)
Preterm delivery (<37 weeks)	1.3 (1.0–1.6)	1.2 (0.9–1.5)	1.3 (1.1–1.6)	1.1 (0.7–1.7)
Parity	1.2 (1.0–1.5)	0.9 (0.7–1.3)	1.1 (0.8–1.4)	—
No receipt of ARVs during pregnancy	—	—	2.0 (0.6–7.2)	1.6 (0.2–15.2)
Receipt of ART or ZDV during pregnancy, but stopped postpartum	—	—	0.9 (0.4–2.5)	1.7 (0.6–5.1)
On ART >2 years before delivery	—	—	0.8 (0.3–2.2)	—
CD4 count during pregnancy	—	—	1.0 (1.0–1.0)	1.0 (1.0–1.0)

^aFor analysis of risk factors of mortality among all study participants, we adjusted for HIV status, presence of an infant birth injury, maternal age, availability of a latrine, housing type, Rh factor, preterm delivery, and parity.

^bFor analysis of risk factors of mortality among only HIV-infected women, we adjusted for infant birth injury, availability of a latrine, housing type, Rh factor, preterm delivery, antiretroviral use, and CD4 count (in pregnancy).

ART, antiretroviral therapy; ARV, antiretroviral medication; ZDV, zidovudine.

including 12 deaths among HIV-infected and 2 deaths among HIV-uninfected women, and 9 (38%) deaths occurred between 12 and 24 months, including 7 deaths among HIV-infected and 2 deaths among HIV-uninfected women (Fig. 1).

Older maternal age, lack of an indoor toilet, informal housing, negative Rh factor, preterm delivery, and higher parity were associated with an increased risk of mortality in univariate analysis. In adjusted analyses, including all of these covariates, HIV-infected women were five times more likely to die by 24 months than HIV-uninfected women (aHR 5.0, 95% CI 1.6–15.2). The only other independent risk factor for maternal death was infant birth injury (aHR 3.8, 95% CI 1.3–11.4) (Table 2). In 3 of the 26 maternal deaths (12.5%), child death followed maternal death.

Among the 22 HIV-infected women who died in the 24-month postpartum period, 3 (14%) never initiated ARVs during pregnancy or during follow-up, 13 (59%) were on 3-drug ART in pregnancy and continued throughout the follow-up period, and 6 (27%) were on ZDV-monotherapy in pregnancy, which was discontinued postpartum (2 of these women subsequently started 3-drug ART in the postpartum period). Compared with women who received 3-drug ART in pregnancy and continued throughout follow-up, there was a nonsignificant increase in mortality among women who received ART or ZDV in pregnancy and stopped postpartum (aHR 1.7, 95% CI 0.6–5.1) and women who received no ART in pregnancy (aHR 1.6, 95% CI 0.2–15.2). Median CD4 cell count was 421 cells/mm³, and CD4 cell count in pregnancy was not associated with mortality ($p=0.20$). Median duration of ART in pregnancy was 100 days, and women on ART before delivery for ≥ 2 years had a similar mortality rate as women on ART for <2 years ($p=0.87$).

Discussion

This is the largest evaluation of the impact of HIV on 24-month postpartum mortality that has been performed in sub-Saharan Africa since 3-drug ART became widely available for

PMTCT and maternal treatment. Almost 90% of our study participants received ARVs (ART or ZDV-monotherapy) in pregnancy in accordance with Botswana's national guidelines, and ART in pregnancy (65%) or in the 24 months postpartum (79%) was high. Given the extensive ART availability, our finding that mortality was five times higher among HIV-infected women than HIV-uninfected women was surprising and highlights an ongoing health disparity between HIV-infected and HIV-uninfected postpartum women.

The overall mortality rate among women in our study was lower than that reported in other African countries among both HIV-infected and HIV-uninfected women.^{1,2,9,10} Although our study may have underestimated mortality in the immediate postpartum period (because women who were sick postpartum may have been less likely to agree to participate), our results are consistent with WHO estimates that show Botswana has a lower maternal mortality ratio than other countries in the region.¹¹ Botswana has relatively higher healthcare expenditure, higher levels of antenatal care, and more in-hospital deliveries than the Southern African region as a whole.¹¹ Despite this overall mortality, 24-month mortality rate for HIV-infected women was higher than for HIV-uninfected women, including for women on ART with relatively preserved CD4 cell counts.

A recent study of women in Uganda¹² found that incident pregnancy may increase the risk of mortality among HIV-infected women, but not all studies have found a similar effect.^{13–15} It is unknown if the increased mortality among HIV-infected women in our cohort was from HIV alone or was enhanced by the recent pregnancy. Predicting this expected mortality for women in our study is challenging; most mortality data are from studies that include pregnancy and delivery followed only through the early postpartum period or from studies of HIV-infected nonpregnant women enrolled at ART initiation with lower median CD4 counts than in our study. In addition, HIV severity decreases fertility, and mortality among nonpregnant HIV-infected women may be higher than among postpartum women.³ One study from

Botswana found mortality at 10–12 months post ART initiation of 670 deaths per 100,000 p-y among HIV-infected men and women enrolled in the national treatment program in 2009.¹⁶ Women in this study were reported to have overall “lower” rates of mortality than men (not further quantified) and a median CD4 count of 161 cells/mm³ at the start of enrollment. Given the high percentage of women on a stable ART regimen at enrollment with high CD4 counts, and the more recent years of enrollment (2012–2013), we would expect an overall mortality among HIV-infected women in our study to be lower than 750 deaths per 100,000 p-y; therefore we believe it is possible that additional risk may have been specific to the postpartum period.

Identifying specific risk factors for mortality in our study was a challenge, as we were not able to collect detailed information on cause of maternal death. Women who stopped ARVs in the postpartum period and did not restart (in accordance with WHO Option B guidelines) had nearly a twofold higher risk of mortality, suggesting that reliance on serial CD4 count measurements may not be adequate to monitor the health of HIV-infected individuals not yet eligible for ART (the “CD4 safety net”),¹⁷ but this finding was not statistically significant. It will be important to reevaluate maternal outcomes as Botswana moves to an Option B+ strategy for PMTCT and more women remain on ART throughout the postpartum period. Interestingly, CD4 count did not predict mortality, although our study was limited to CD4 count taken during pregnancy. We cannot say if CD4 decline in the postpartum period may have been an important factor in maternal deaths. Women in Botswana likely have less contact with the healthcare system in the postpartum period than in the antenatal period, and further investigation is needed to determine if lack of medical care or other factors contributed to higher mortality.

Our finding of an increased risk of maternal death following deliveries with infant birth injury is of unclear significance. Birth injuries were rare (6.0%), and more than 80% of the infant birth injuries reported were “caput succedaneum” (swelling of the scalp), including all infant birth injuries followed by maternal death ($N=4$, 15.4%). While this could be a proxy for obstructed labor, which increases maternal mortality,¹⁸ none of these four women required a C-section and all four maternal deaths occurred in the second year of follow-up. Therefore, it seems most likely that this finding is a statistical anomaly.

Strengths of our study included the high rate of follow-up achieved; the study design to minimize the influence of the study on the outcome of mortality; the setting of Botswana with a mature HIV program; and high levels of access to ART and PMTCT. The major limitation of our study was the lack of detailed information on new medical problems, ART adherence, and on the cause of maternal death. In addition, there were notable differences in maternal demographic characteristics and socioeconomic markers by HIV status. All of these factors may have had an impact on maternal health, making it difficult to understand the exact relationship among HIV, ART, and postpartum mortality. We attempted to account for these differences using adjustment in multivariate analyses, but there may still be bias from unmeasured confounding. Although mortality rates in our study are specific to Botswana, our results may be generalizable to settings with widespread ART uptake and relatively preserved CD4 cell

counts. Postpartum retention in HIV care and ART adherence in the postpartum period affect HIV-infected women universally around the globe.^{19–23}

Conclusions

In summary, our results suggest that even when ART is widely available in the setting of an Option B PMTCT program, HIV-infected women are at particularly high risk of death in the postpartum period. Starting (and continuing) ART at higher CD4 counts, and closer clinical monitoring of postpartum HIV-infected women in the 24-months postpartum, could improve maternal outcomes.

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Author Disclosure Statement

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