Predictive Value of Weight Loss on Mortality of HIV-Positive Mothers in a Prolonged Breastfeeding Setting

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Abstract

HIV-positive lactating women may be at high risk of weight loss due to increased caloric requirements and postpartum physiological weight loss. Ten percent weight loss is associated with a higher risk of mortality in HIV-positive patients and this alone is a criterion for highly active antiretroviral therapy (HAART) initiation where CD4 counts are not available. However, no study has investigated this association in lactating postpartum women. We investigated whether 10% weight loss predicts death in postpartum HIV-positive women. A total of 9207 HIV-negative and 4495 HIV-positive mothers were recruited at delivery. Women were weighed at 6 weeks, 3 months, and every 3 months thereafter for up to 24 months postpartum and data on mortality up to 2 years were collected. The median duration of breastfeeding was longer than 18 months. Among HIV-positive women, the independent predictors of $\geq 10\%$ weight loss were CD4 cell count, body mass index, and household income. Mortality was up to 7.12 (95% CI 3.47–14.61) times higher in HIV-positive women with $\geq 10\%$ weight loss than those without weight loss. Ten percent weight loss in postpartum lactating HIV-positive women was significantly predictive of death. Our findings suggest that 10% weight loss is an appropriate criterion for HAART initiation among postpartum breastfeeding women.

Introduction

WEIGHT LOSS IS A STRONG risk factor for death in HIV-positive people living in food-secure, industrialized country populations,^{1–5} where it is usually due to increased basal metabolic rate,⁶ the antitrophic effects associated with opportunistic infections,^{7–9} malabsorption,⁷ decreased dietary intake associated with anorexia,¹⁰ and metabolic abnormalities.¹¹ Accordingly, the World Health Organization (WHO) guidelines for highly active antiretroviral therapy (HAART) state that when CD4 count is not available, $\geq 10\%$ weight loss alone is a sufficient indication for treatment initiation. However, this recommendation is based on data from studies in developed countries while the majority of HIV-infected individuals (and nearly all those for whom CD4 is not available) live in developing countries, where many other factors besides HIV could contribute to weight loss and where less information on the association between weight loss and mortality is available.¹² Consequently, the weight loss indicator is not widely used in programs as a sole indicator for HAART initiation due to concern that it may be too sensitive in developing country settings¹³ and lead to premature initiation of

HAART, which is associated with a waste of resources, adverse events, pill fatigue, noncompliance, and the emergence of resistant virus strains.¹⁴ There may be particular reluctance to rely on weight loss alone for postpartum lactating women in whom weight loss is expected due to physiological postpartum weight loss and the high energy demands of lactation¹⁵ estimated to be 467–600 kcal/day between 0 and 23 months postpartum.^{16–18} Among HIV-positive lactating mothers in Africa, longer breastfeeding duration was associated with less postpartum weight gain¹⁹ and breastfeeding increased the risk of weight loss compared to formula feeding.²⁰ Furthermore, exclusive breastfeeding requires more caloric intake than partial breastfeeding,¹⁶ but is the optimal feeding method for all babies during the first 6 months of life, including HIV-exposed infants.²¹

However, since weight loss can be identified without sophisticated diagnostic devices or a high level of training, it would be a highly valuable tool in identifying HAART eligibility in resource-limited settings if it is predictive of death. This analysis was conducted among HIV-negative and HIV-positive women enrolled in the ZVITAMBO trial in Harare, Zimbabwe. Mortality at 24 months was 2.3/1000

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person-years and 38.3/1000 person-years among HIV-negative and HIV-positive women, respectively.²² The objective of the current article is to describe their weight loss pattern, identify risk factors for postpartum weight loss, and determine whether a $\geq 10\%$ weight loss over this period was a significant predictor of mortality.

Materials and Methods

Details of the ZVITAMBO trial have been previously published.^{22–24} Briefly, 14,110 mother–infant pairs were recruited within 96 h of delivery between November 1997 and January 2000 in Harare, Zimbabwe. Mothers and infants were included in the study if neither had an acutely life-threatening condition and the mother had planned to stay in Harare after recruitment. Written informed consent was obtained. Hospital records, questionnaires, and direct measurements were used to obtain baseline information. Follow-up was conducted at 6 weeks, 3 months, and then every 3 months up to 12 to 24 months. HIV-positive mothers and their infants were initially planned to be followed for 24 months. However, in June 2000, economic conditions necessitated discontinuing the second year of follow-up. Thus 24%, 48%, and 100% of the pairs were reassigned to 24 months, ≥ 18 months, and ≥ 12 months follow-up, respectively. Of the HIV-negative mothers, 4632 and 4930 were initially randomized to complete the study after 12 and 24 months of follow-up, respectively, and in June 2000, 24%, 48%, and 100% of the 4930 were reassigned to 24 months, ≥ 18 months, and ≥ 12 months follow-up, respectively. Antiretroviral drugs were not available in Harare during the study period. At baseline, women were tested for HIV by an algorithm incorporating two parallel ELISAs and Western blot.²⁴ Plasma CD4 cells were counted by FACScount (Becton Dickinson) and were available in 36% of the HIV-negative women and 87% of the HIV-positive women. Plasma viral load was measured in 36% of HIV-positive women (Roche Amplicor). Hemoglobin (Hb) was measured in women enrolled from October 1, 1998 to the end of the study (approximately 60% of the mothers) by HemoCue (Mission Viejo, CA). Height (Height-Rite stadiometer, model 225, Seca, Hanover, MD) was measured at the first follow-up visit, and weight (balance beam scale model 700, Seca, Hanover, MD) at all follow-up visits but not at baseline. Body mass index (BMI) was calculated as weight (kg)/[height (m)]². Information on breastfeeding status and subsequent pregnancy was obtained by self-report at follow-up visits.

Statistical analysis

Statistical analysis was conducted using Stata Version 9.2 (StataCorp LP, Texas). Baseline characteristics were examined by chi-square tests for categorical variables and Kruskal–Wallis tests for continuous variables between HIV-negative and HIV-positive women. The rate of breastfeeding at 12, 18, and 24 months was calculated using the Kaplan–Meier (K-M) method. The women were censored on the date of weaning, if known, or at the last date in which they were known to be breastfeeding.

Postpartum weight change patterns between HIV-negative and HIV-positive women

To describe the postpartum weight change pattern as accurately as possible, we restricted the study population for this part of the analysis in three ways: (1) we included only

mothers who had weight measured at 24 months to avoid follow-up bias; (2) we excluded women who became pregnant during follow-up to eliminate the effect of subsequent pregnancy on weight loss pattern; and (3) we included only weight measurements that were conducted within ± 7 days of the scheduled date of follow-up to obtain an accurate estimate of weight and weight difference at each time point. Kruskal–Wallis tests were used to compare the median weight and median weight change from 6 weeks between HIV groups. Wilcoxon sign rank tests were used to test median weight change from 6 weeks within each HIV group against 0.

Cumulative risk of $\geq 10\%$ weight loss relative to weight at 6 week postpartum in HIV-negative and HIV-positive women, and predictors of $\geq 10\%$ weight loss in HIV-positive women

K-M methods were used to estimate the cumulative risk of $\geq 10\%$ weight loss in HIV-negative and HIV-positive women between 6 weeks and 2 years postpartum. All women who had weight measured within ± 7 days of the scheduled date at 6 weeks and at one or more subsequent time points were included in this analysis. This analysis was not restricted to those with weight measurement within ± 7 days of the scheduled follow-up visit date after the 6-week visit. Women were censored at the date on which a $\geq 10\%$ weight loss was detected or at the date of their last weight measurement. We compared the time to weight loss between HIV groups using the Cox regression model. Univariate Cox regression models were used to identify independent risk factors for experiencing a $\geq 10\%$ weight loss in HIV-positive women. A multivariate Cox model was constructed by stepwise selection of variables (with entry and retention levels of $p = 0.10$ and 0.05 , respectively) to identify influential covariates. The factors offered to the model were maternal BMI at 6 weeks, plasma CD4 cell count, plasma HIV-RNA, age, enrollment date, marital status, parity, hemoglobin, education, occupation, and household income.

Cumulative mortality risk by $\geq 10\%$ weight loss in HIV-positive women

K-M methods were used to compare the cumulative maternal mortality risk for HIV-positive women who had and had not experienced a $\geq 10\%$ weight loss during 10 different intervals (6 weeks and 3, 6, 9, 12 months; 3 months and 6, 9, 12 months; 6 months and 9 and 12 months; 9 months and 12 months). Only women who had weight measured at both time points within ± 7 days of the scheduled follow-up date were included in these analyses. Mortality risk after the latter of the two weight measurements was calculated by a Cox proportional hazards model. Risk factors of mortality were identified by stepwise selection of variables with entry and retention levels of $p = 0.10$ and 0.05 , respectively, in a Cox regression hazards model. Maternal BMI at 6 weeks, plasma CD4 cell count, plasma HIV-RNA, age, enrollment date, marital status, parity, hemoglobin, education, occupation, and household income and a binary variable of ever having $\geq 10\%$ weight loss in respect to weight at 6 weeks (± 7 days) were offered to the model.

TABLE 1. MATERNAL BASELINE CHARACTERISTICS BY MATERNAL HIV INFECTION STATUS

Characteristics	Category	HIV–	%	HIV+	%	p-value
Age (years)	<20	827	(20.3)	238	(10.7)	<0.001
	20–34	2883	(70.8)	1803	(80.9)	
	>34	362	(8.9)	188	(8.4)	
	Median (IQR)*	23.6	(20.5–27.8)	25.4	(22.2–29.3)	
Plasma CD4 (cells/ μ l)	<350	25	(7.9)	789	(40.5)	<0.001
	$\geq$ 350	293	(92.1)	1157	(59.5)	
	Median (IQR)*	737	(529–961)	399	(251–559)	
Plasma HIV-1 RNA (copies/ml)	$\leq$ 500	—	—	29	(3.4)	<0.001
	501–10,000	—	—	356	(41.1)	
	10,001–40,000	—	—	229	(26.4)	
	>40,000	—	—	252	(29.1)	
Hemoglobin (g/liter)	<70	39	(1.5)	40	(3.1)	<0.001
	70–120	1138	(44.8)	829	(63.3)	
	>120	1366	(53.7)	441	(33.7)	
BMI at 6 weeks (kg/m ²)	<18.5	179	(4.5)	118	(5.4)	0.001
	18.5–24.9	2684	(67.3)	1533	(70.6)	
	$\geq$ 25.0	1127	(28.3)	521	(24.0)	
	Median (IQR)*	23.0	(20.9–22.6)	22.6	(20.7–24.9)	
Marital status	Married/stable	3857	(94.8)	2037	(91.7)	<0.001
	Separated/widowed	58	(1.4)	84	(3.8)	
	Single-never married	152	(3.7)	101	(4.6)	
Occupation	Unemployed	3322	(81.6)	1784	(80.1)	0.320
	Domestic worker	225	(5.5)	127	(5.7)	
	Other	525	(12.9)	316	(14.2)	
Household income per month (US\$) ^a	<130	2374	(74.7)	1219	(75.1)	0.772
	$\geq$ 130	803	(25.3)	404	(24.9)	
Parity	1	1647	(40.4)	570	(25.5)	<0.001
	2–4	2113	(51.8)	1513	(67.8)	
	$\geq$ 5	320	(7.8)	150	(6.7)	
Education (years)	0–7	729	(17.9)	432	(19.4)	0.154
	8–13	3342	(82.1)	1799	(80.6)	
Enrollment date	16 Jul 1999–31 Jan 2000	1237	(30.3)	632	(28.3)	0.153
	1 Jan 1999–15 Jul 1999	965	(23.7)	507	(22.7)	
	16 Jun 1998–31 Dec 1998	988	(24.2)	580	(26.0)	
	25 Nov 1997–15 Jun 1998	890	(21.8)	514	(23.0)	
Breastfeeding status at 3 months (previous 7 days)	Exclusive	551	(10.3)	258	(10.2)	0.092
	Predominant	1892	(35.2)	833	(32.8)	
	Mixed	2929	(54.5)	1446	(57.0)	

Restricted to women who had weight measurement at 42 days ($\pm$ 7 days) and at least one subsequent weight measurement.

^aInflation adjusted.

IQR, interquartile range; p-value calculated by chi-square apart from values marked with an asterisk (*) that are tested by Kruskal–Wallis test; data, n (%) unless otherwise stated.

Ethical approval

Ethical approval was granted from the Medical Research Council of Zimbabwe, Medicines Control Authority of Zimbabwe, the Committee on Human Research of the Johns Hopkins University Bloomberg School of Public Health, and the Ethics Committee of the Research Institute of the McGill University Health Center.

Results

A total of 9207 women were HIV negative at baseline and never seroconverted and 4495 tested HIV positive at baseline. The rate of breastfeeding at 12, 18, and 24 months among HIV-negative women was 96.5%, 56.9%, and 16.5%, respectively, and among HIV-positive women was, respectively, 90.5%, 46.7%, and 13.0%. The age of weaning [median (IQR)] was 578 (515–661) and 548 (486–639) days for HIV-negative and HIV-positive women, respectively. The baseline characteristics of the HIV-negative and HIV-positive women who had weight

measurement at 42 days ($\pm$ 7 days) and at least one subsequent weight measurement are illustrated in Table 1. In the HIV-positive population, the CD4 cell count [median (IQR)] was 399 (251–559). HIV-positive women were older with higher parity and more likely to be widowed or separated compared to HIV-negative women. Overweight was common where 28.3% and 24.0% of HIV-negative and HIV-positive women, respectively, had a BMI $\geq$ 25.

Postpartum weight change patterns between HIV-negative and HIV-positive women

A total of 625 HIV-negative and 561 HIV-positive women who were weighed within $\pm$ 7 days of the scheduled date of follow-up at 24 months without subsequent pregnancy were included in the analysis. The [median (IQR)] weight was 60.0 (53.9–67.0) kg and 58.5 (52.8–65.5) kg for HIV-negative and HIV-positive women at 6 weeks postpartum, respectively (Fig. 1 and Table 2). After 6 weeks, median weight declined

FIG. 1. Median weight at follow-up in HIV-negative and HIV-positive women. Only women who had weight measured at 24 months (within ± 7 days of the scheduled visit) and did not become pregnant are included. Only weight measurements conducted within ± 7 days of the scheduled follow-up date are included. Differences between HIV-negative and HIV-positive women are statistically significant at 6 weeks, 6 months, 15 months, 18 months, 21 months, and 24 months ($p < 0.05$, Kruskal-Wallis test).

among both HIV-negative and HIV-positive women reaching nadirs of 57.4 kg (IQR: 51.0–65.3) at 12 months and 56.0 kg (IQR: 51.0–62.5) at 18 months, respectively, before increasing to 58.5 kg (IQR: 53.0–65.9) and 57.4 kg (IQR: 51.4–63.8), respectively, at 24 months. The median weight of HIV-positive women was significantly lower than that of HIV-negative women at all time points except at 3 months, 9 months, and 12 months. The change in weight between 6 weeks and all subsequent time points was not significantly different between HIV groups for any of the intervals.

Cumulative risk of $\geq 10\%$ weight loss relative to weight at 6 weeks postpartum in HIV-negative and HIV-positive women

A total of 4078 HIV-negative and 2233 HIV-positive women for whom weight was available at 6 weeks (± 7 days) with at least one subsequent time point were included in the analysis. The cumulative risks (95% CI) of $\geq 10\%$ weight loss relative to weight at 6 weeks among HIV-negative women were 15.5% (14.4–16.7%) and 34.1% (31.5–36.9%) at 365 and 730 days, respectively. The comparable values for HIV-positive women were 17.4% (15.8–19.2%) and 38.0% (35.3–40.9%). The cumulative probability of attaining $\geq 10\%$ weight loss was 25% at 457 and 468 days for HIV-positive and HIV-negative women, respectively. Among women who experienced $\geq 10\%$ weight loss between 6 weeks and 12 months, the median (IQR) weight loss for HIV-positive and HIV-negative women was 5.7 (3.1–8.3) kg and 6.3 (4.0–8.4) kg, respectively. The corresponding values for women who experienced $\geq 10\%$ weight loss between 6 weeks and 24 months were 4.0 (3.0–7.0) kg and 3.7 (0.8–7.0) kg. HIV-positive women were 14% (HR 95% CI 1.02–1.27; $p = 0.018$) more likely to lose at least 10% of their body weight than HIV-negative women. After adjustment for BMI at 6 weeks, household income, age, and education, this association remained similar (data not shown).

Predictors of $\geq 10\%$ weight loss in HIV-positive women

In univariate analyses, BMI < 18.5 at 6 weeks, CD4 < 350 cells/ μ l at delivery, monthly income $< US\$130$, and schooling

< 7 years were significant predictors of subsequent $\geq 10\%$ weight loss among HIV-positive women (Table 3). In the final Cox model, only CD4 at baseline, BMI at 6 weeks, and household income were retained. Lower household income was associated with a 55% higher risk of weight loss. Those with BMI < 18.5 were 45% less likely to have weight loss but those with BMI ≥ 25 had a 26% higher risk of weight loss compared to those with BMI 18.5–24.9.

Cumulative maternal mortality risk among HIV-positive women with and without $\geq 10\%$ weight loss

HIV-positive women who lost $\geq 10\%$ of their body weight during any of the 10 intervals examined were at a 1.9–7.1 times higher risk of subsequent death compared to HIV-positive women who did not experience weight loss of this magnitude during the same interval (Table 4). This greater risk was statistically significant for 7 of the 10 times intervals. There were no distinct patterns in the risk of mortality associated with weight loss of an acute or chronic nature.

Baseline CD4, BMI, education, and ever having had $\geq 10\%$ weight loss emerged as significant predictors of maternal mortality. After adjustment for CD4, education, and weight loss, BMI < 18.5 was associated with a 3.24 (95% CI 1.62–6.48; $p = 0.001$) times higher risk of death compared to BMI 18.5–24.9, but BMI ≥ 25 conferred no significant protective effect compared to BMI 18.5–24.9 [HR 0.74 (95% CI 0.39–1.40; $p = 0.355$).

Discussion

In this study, 34.1% of HIV-negative and 38.0% of HIV-positive women lost at least 10% of their body weight between 6 weeks and 24 months postpartum. Yet despite this high background rate of weight loss, HIV-positive postpartum breastfeeding women who lost $\geq 10\%$ of their body weight during any of the 10 time intervals between 6 weeks and 24 months postpartum were at substantially higher risk of death compared with similar women who did not experience this weight loss during the same time interval. Significant independent predictors of experiencing a $\geq 10\%$ weight loss in HIV-positive women were BMI, CD4, and household income. Compared to women with a 6 week BMI 18.5–24.9, women with BMI ≥ 25 had a 26% higher risk of weight loss and women with BMI < 18.5 had a 45% lower risk of a $\geq 10\%$ weight loss. To investigate whether there was detection bias of weight loss in those with BMI < 18.5 because they were too sick to have weight measured, sensitivity analysis was conducted by excluding women who died but results remained similar (data not shown). It has been reported that larger gestational weight gain is associated with more postpartum weight loss²⁵ and this result might be reflecting this phenomenon. Women whose household income was in the higher quartile were protected from weight loss. It might have been that poorer women had economic difficulties obtaining food that could fulfill the increased caloric demand of breastfeeding. Also, higher income women may have had more medical attention and access to drugs to control opportunistic infections that lead to weight loss, and/or more sedentary life styles with lower caloric requirements. The relationship between CD4 and weight loss is most likely mediated by the characteristics of advanced HIV infection such as higher risk of opportunistic infections,^{7–9} malabsorption,⁷ and abnormal metabolism,¹¹ which all contribute to weight loss.

TABLE 2. POSTPARTUM WEIGHT CHANGE IN HIV-NEGATIVE AND HIV-POSITIVE WOMEN

	6 weeks	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months
HIV⁻									
Weight (kg)									
Median	60.0	58.7	59.1	58.0	57.4	57.8	57.6	58.0	58.5
(IQR)	(53.9–67.0)	(53.4–66.2)	(53.0–66.0)	(52.0–66.0)	(51.0–65.3)	(52.0–65.0)	(51.5–64.9)	(52.0–65.6)	(53.0–65.9)
N	419	519	548	538	588	595	549	568	625
Difference from 6 weeks (kg)									
Median		-0.2	-0.2	-1.3 ^a	-1.3 ^a	-1.4 ^a	-1.2 ^a	-1.5 ^a	-1.0
(IQR)		(-1.5–1.0)	(-2.8–2.2)	(-3.6–1.5)	(-4.2–2.2)	(-4.0–2.2)	(-4.4–2.0)	(-4.0–1.6)	(-3.5–3.0)
N		334	319	301	320	327	303	301	327
HIV⁺									
Weight (kg)									
Median	58.5 ^b	58.0	57.7 ^b	57.4	56.2	56.3 ^b	56.0 ^b	56.0 ^b	57.4 ^b
(IQR)	(52.8–65.5)	(52.1–65.0)	(52.0–64.4)	(51.5–64.4)	(51.0–63.0)	(51.0–62.4)	(51.0–62.5)	(50.7–62.8)	(51.4–63.8)
N	448	505	497	527	529	546	526	520	561
Difference from 6 weeks (kg)									
Median		-0.5 ^a	-0.5 ^a	-0.9 ^a	-1.6 ^a	-2.0 ^a	-1.5 ^a	-1.6 ^a	-1.0 ^a
(IQR)		(-1.8–1.0)	(-2.9–1.6)	(-3.7–1.5)	(-4.4–1.1)	(-4.5–1.1)	(-4.7–1.8)	(-5.0–2.0)	(-4.0–2.8)
N		366	340	343	334	342	328	316	331

Only women who had weight measured at 24 months (within ± 7 days of scheduled visit) and did not become pregnant again during follow-up are included. Only weight measurements conducted within ± 7 days of scheduled follow-up date are included.

^aSignificantly different from 0 by the Wilcoxon sign rank test ($p < 0.05$).

^bMedian weight significantly different from HIV negative by the Kruskal–Wallis test ($p < 0.05$).

Weight difference from 6 weeks was not significantly different between HIV groups at any of the follow-ups by the Kruskal–Wallis test ($p \geq 0.05$).

TABLE 3. UNIVARIATE AND MULTIVARIATE COX PROPORTIONAL HAZARDS MODELS FOR $\geq 10\%$ WEIGHT LOSS BETWEEN 6 WEEKS AND 24 MONTHS IN HIV-POSITIVE WOMEN

Baseline characteristic	Category	n	HR ^a	95% CI	p-value	Adj HR ^b	95% CI	p-value
Plasma CD4 count (cells/ μ l)	≥ 350	1157	1.00			1.00		
	<350	789	1.33	(1.12–1.59)	0.001	1.38	(1.16–1.65)	<0.001
Household income/month(US\$) ^c	≥ 130	404	1.00			1.00		
	<130	1219	1.50	(1.17–1.91)	0.001	1.55	(1.21–1.97)	<0.001
BMI at 6 weeks postpartum ^d	18.5–24.9	1533	1.00			1.00		
	<18.5	118	0.57	(0.35–0.93)	0.024	0.55	(0.34–0.89)	0.016
	≥ 25.0	521	1.19	(0.99–1.44)	0.063	1.26	(1.04–1.52)	0.016
Plasma HIV-1 RNA (copies/ml)	≤ 500	29	1.00					
	501–10,000	356	1.73	(0.70–4.26)	0.232			
	10,001–40,000	229	1.47	(0.59–3.68)	0.405			
	>40,000	252	2.07	(0.84–5.12)	0.114			
Enrollment date	16 Jul 1999–31 Jan 2000	632	1.00					
	1 Jan 1999–15 Jul 1999	507	0.79	(0.60–1.03)	0.081			
	16 Jun 1998–31 Dec 1998	580	0.92	(0.72–1.18)	0.504			
	25 Nov 1997–15 Jun 1998	514	0.82	(0.64–1.06)	0.138			
Age (years)	20–34	1803	1.00					
	<20	238	0.77	(0.58–1.02)	0.070			
	>34	188	0.96	(0.72–1.28)	0.786			
Marital status	Married/stable	2037	1.00					
	Separated/widowed	84	0.83	(0.52–1.33)	0.440			
	Single-never married	101	0.88	(0.58–1.32)	0.525			
Parity	1	570	1.00					
	2–4	1513	0.97	(0.80–1.17)	0.767			
	≥ 5	150	1.09	(0.78–1.52)	0.606			
Hemoglobin (g/liter)	70–120	829	1.00					
	<70	40	1.08	(0.53–2.19)	0.841			
	>120	441	1.16	(0.90–1.49)	0.245			
Education (years)	>7	1799	1.00					
	≤ 7	432	1.24	(1.02–1.51)	0.034			
Occupation	Unemployed	1784	1.00					
	Domestic worker	127	1.03	(0.73–1.47)	0.851			
	Other	316	0.88	(0.69–1.12)	0.305			

^aUnivariate hazards ratio.^bAdjusted for baseline CD4 cell count, BMI at 6 weeks, and household income.^cInflation adjusted.^dBMI (body mass index). Calculated as weight (kg)/[weight (m)]².

The observation that weight loss is associated with poor survival is in accordance with previous studies, which were all conducted in developed countries. First, in a group of mainly but not restricted to gay white men, $\geq 10\%$ weight loss over a period of 4 months in HIV-positive individuals was associated with a 2.54 time higher risk of death when compared to those without this magnitude of weight loss.³ Similarly, in another study, body weight of $<90\%$ of self-reported usual weight was associated with a 8.3 (95% CI 2.3–34.1) times higher risk of death.¹ Third, 10% weight loss from near the time of first AIDS diagnosis was associated with a 6.7 (95% CI 5.2–8.6) times higher mortality.⁵ Finally, a weight loss of ≥ 4.5 kg between 3 and 9 months before development of AIDS was associated with a significantly shorter survival (median 1.06 vs. 1.45 years) compared to those without this magnitude of weight loss in gay men.²

Since weight loss is a simple measure that does not necessitate sophisticated diagnostic facilities or trained personnel, it may be a useful adjunct to CD4 or viral load estimations in assessing HAART eligibility in resource-limited settings. Although weight loss was a significant predictor of mortality in our study, it has been pointed out that weight loss alone may be too sensitive for HAART eligibility¹³ and its utility as a HAART

eligibility criterion must be assessed. The predictive value of weight loss on risk of disease progression or death must be compared to other conditions of HAART eligibility that can easily be identified in resource-limited settings. Furthermore, the inclusion of other conditions such as anemia, low BMI, presence of fever, diarrhea, or oral candidiasis with weight loss may further improve detection of those who are truly in need of HAART and this requires further investigation. Also, the WHO definition of 10% weight loss does not specify the timeframe in which weight loss occurs.¹² In our study, the highest hazard rate of death was observed in those who had weight loss over a short period of time (between 6 weeks and 3 months), but we could not detect a distinct pattern in the relationship between death and weight loss of an acute and chronic nature.

In this study, the peak weight loss was at 15 months (–2.0 kg) and 21 months (–1.5 kg) for HIV-positive and HIV-negative women, respectively. Two studies in Africa have reported postpartum weight change among lactating women. The first one from South Africa reported a 1.4 kg weight loss in HIV-positive women and a 0.4 kg weight gain in HIV-negative women between 8 and 24 weeks²⁶ and another study from Zambia reported a 1.1 kg weight gain between 4 and 24 months among HIV-positive women who breastfed for a median of 16

TABLE 4. MORTALITY IN HIV-POSITIVE WOMEN BY THE PRESENCE OF $\geq 10\%$ WEIGHT LOSS

Mortality	$\geq 10\%$ weight loss between	Total N	Median (IQR) weight change (kg)	%CD4 <350 cells/ μL^a	Number of deaths	HR	95% CI	p-value
3–24 months	6 weeks and 3 months							
	No	1706	−0.5 (−1.8 to 0.9)	39.6	43	1.00		
	Yes	51	−9.5 (−12.8 to −6.7)	53.5	9	7.12	(3.47–14.61)	<0.001
6–24 months	6 weeks and 6 months							
	No	1446	−0.7 (−2.6 to 1.5)	38.5	23	1.00		
	Yes	114	−7.9 (−10.3 to −6.7)	41.4	9	5.03	(2.33–10.86)	<0.001
	3 months and 6 months							
	No	1631	−0.2 (−1.8 to 1.4)	38.2	26	1.00		
	Yes	55	−8.0 (−10.3 to −6.7)	46.0	4	4.84	(1.69–13.86)	0.003
9–24 months	6 weeks and 9 months							
	No	1340	−0.9 (−3.0 to 1.5)	38.4	21	1.00		
	Yes	146	−8.0 (−10.0 to −6.7)	47.7	7	3.18	(1.35–7.47)	0.008
	3 months and 9 months							
	No	1454	−0.6 (−2.5 to 1.5)	38.6	16	1.00		
	Yes	92	−7.9 (−9.8 to −6.8)	45.7	5	5.28	(1.93–14.42)	0.001
	6 months and 9 months							
	No	1615	−0.3 (−1.8 to 1.2)	39.4	25	1.00		
	Yes	43	−9.0 (−12.0 to −7.0)	51.4	1	1.91	(0.26–14.14)	0.526
12–24 months	6 weeks and 12 months							
	No	1255	−1.0 (−3.1 to 1.9)	39.6	13	1.00		
	Yes	196	−8.4 (−10.6 to −6.9)	38.6	5	2.27	(0.81–6.38)	0.119
	3 months and 12 months							
	No	1368	−0.8 (−2.9 to 1.6)	37.7	9	1.00		
	Yes	129	−7.7 (−10.0 to −6.7)	43.4	6	6.08	(2.16–17.09)	0.001
	6 months and 12 months							
	No	1440	−0.5 (−2.3 to 1.8)	38.8	12	1.00		
	Yes	100	−8.0 (−10.3 to −6.8)	52.9	3	3.44	(0.97–12.19)	0.056
	9 months and 12 months							
	No	1602	−0.2 (−1.8 to 1.3)	39.9	16	1.00		
	Yes	56	−8.5 (−10.0 to −6.9)	43.2	3	6.17	(1.80–21.19)	0.004

Only women who had weight measurements at both time points and within ± 7 days of the scheduled visit date are included.

^aCD4 cell count at baseline.

IQR, interquartile range.

months.¹⁹ Our results showed a median weight loss of 0.5 kg (HIV-positive women) and 0.2 kg (HIV-negative women) between 6 weeks and 6 months and no weight gain between 3 and 24 months among HIV-positive women. The reason why the weight change pattern between previous studies and ours differs is unclear, but the study from South Africa had a small sample size and thus this may be attributable to random variation.

We had three major limitations. First, the longest interval for weight measurement in our study was between 6 weeks and 12 months, so we were limited to weight loss that occurred within less than a year in our analyses. Future studies would be necessary to determine whether there is a difference in risk of death associated with acute and chronic weight loss with a longer follow-up period. Second, we did not have CD4 counts at follow-up. It would be important to investigate the correlation of weight loss with CD4 count (the gold standard for initiation of HAART) at the time of identification of a $\geq 10\%$ weight loss. This is particularly important because nevirapine-based HAART, which is the most common regimen in developing countries, may be more likely to induce hepatotoxicity in

those with high CD4 counts,²⁷ and thus evaluating the range of CD4 counts when a $\geq 10\%$ weight loss is observed would be important. Finally, we did not have weight measurement before and during pregnancy. Since larger gestational weight gain has been reported to be associated with more postpartum weight loss,²⁵ the magnitude of the residual confounding effect of this factor remains unknown.

In conclusion, 10% weight loss after 6 weeks postpartum was predictive of death up to 24 months in HIV-positive women in a prolonged breastfeeding setting. Our findings support the WHO recommendation that HIV-positive people who experience a $\geq 10\%$ weight loss should be initiated on HAART, and provide evidence that this recommendation is specifically applicable for HIV-positive lactating women in developing countries.

Acknowledgments

Ai Koyanagi analyzed the data and wrote the article. Jean Humphrey designed the study and contributed to writing the

article. Robert Ntozini and Lawrence Moulton provided statistical advice. Kuda Mutasa conducted the laboratory work. Peter Iliff and Andrea Ruff contributed to writing the article.

The ZVITAMBO project was supported by the Canadian International Development Agency (CIDA) (R/C Project 690/M3688), United States Agency for International Development (USAID) (cooperative agreement number HRN-A-00-97-00015-00 between Johns Hopkins University and the Office of Health and Nutrition–USAID), and a grant from the Bill and Melinda Gates Foundation, Seattle, WA. Additional funding was received from the Rockefeller Foundation (New York, NY) and BASF (Ludwigshafen, Germany).

Members of the ZVITAMBO Study Group, in addition to the named authors, are: Henry Chidawanyika, John Hargrove, Agnes I. Mahomva, Florence Majo, Lucie C. Malaba, Michael T. Mbizvo, Faith Mzengeza, Kusum J. Nathoo, Mary Ndhlovu, Ellen Piwoz, Lidia Propper, Phillipa Rambanepasi, Naume Tavengwa, Brian J. Ward, Lynn S. Zijenah, Clare D. Zunguza, and Partson Zvandasara.

Author Disclosure Statement

No competing financial interests exist.

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