TABLE 2
Baseline characteristics by breastfeeding practice at 3 mo by the "previous 7 d" definition[1]

	EBF	PBF	MBF	*P* value
Infant characteristics				
Male sex	257 (46.6)	980 (51.6)	1577 (53.6)	0.009[2]
5-min APGAR <8	13 (2.5)	74 (4.0)	107 (3.7)	0.265[2]
Birth weight <2500 g	72 (13.1)	247 (13)	327 (11.2)	0.106[2]
Birth weight (g)	3012.9 ± 480.5[3]	3006.7 ± 464.2	3010.1 ± 443.1	0.978[4]
Gestational age <37 wk[5]	42 (7.7)	132 (7.0)	172 (5.9)	0.136
Mode of delivery not normal vaginal[6]	61 (11.2)	214 (11.4)	319 (11.0)	0.882[2]
Maternal characteristics				
Hemoglobin				0.216[2]
<70 g/L	6 (1.6)	16 (1.6)	26 (1.7)	
70–120 g/L	156 (41.1)	448 (44.1)	737 (47.2)	
>120 g/L	218 (57.4)	553 (54.4)	800 (51.2)	
Marital status				0.535[2]
Married or stable	524 (95.5)	1786 (94.2)	2783 (94.8)	
Separated or widowed	9 (1.6)	29 (1.5)	36 (1.2)	
Single or never married	16 (2.9)	81 (4.3)	118 (4.0)	
Age				0.003[2]
<20 y	98 (17.8)	438 (23.1)	674 (22.9)	
20–34 y	389 (70.5)	1305 (68.9)	2037 (69.3)	
>34 y	65 (11.8)	151 (8.0)	227 (7.7)	
Education <8 y	95 (17.3)	337 (17.8)	531 (18.1)	0.897[2]
Occupation				0.058[2]
Unemployed	444 (80.6)	1607 (84.7)	2405 (81.8)	
Domestic worker	32 (5.8)	84 (4.4)	149 (5.1)	
Other	75 (13.6)	206 (10.9)	387 (13.2)	
MUAC <23 cm[7]	51 (9.3)	219 (11.6)	328 (11.2)	0.311[2]
Parity				<0.001[2]
1	161 (29.2)	879 (46.3)	1329 (45.1)	
2–4	341 (61.8)	887 (46.7)	1414 (48.0)	
≥5	50 (9.1)	134 (7.1)	203 (6.9)	
Vital status of previous child[8]				0.024[2]
Alive	375 (96.2)	956 (94.6)	1497 (92.8)	
Dead	15 (3.9)	55 (5.4)	116 (7.2)	
Religion				0.136[2]
Apostolic or Zion	169 (30.7)	545 (28.7)	880 (29.9)	
Protestant or Catholic	338 (61.3)	1139 (60.0)	1725 (58.6)	
Other	44 (8.0)	214 (11.3)	340 (11.5)	
Other characteristics				
Household income (US$)[9]	79.1 (51.9–136.4)[10]	82.2 (53.9–133.6)	78.5 (50.7–133.6)	0.522[4]
No. of subjects whose household income was available	440	1453	2246	
Paternal education <8 y	38 (7.0)	126 (6.8)	232 (8.1)	0.217[2]
Paternal occupation				0.468[2]
Unemployed	44 (8.1)	136 (7.3)	205 (7.1)	
Domestic worker	158 (29.2)	515 (27.5)	741 (25.6)	
Skilled manual	205 (37.8)	739 (39.4)	1179 (40.7)	
Other	135 (24.9)	484 (25.8)	775 (26.7)	
Date of enrollment				<0.001[2]
25 Nov 1997–15 Jun 1998	106 (19.2)	563 (29.6)	833 (28.3)	
16 Jun 1998–31 Dec 1998	82 (14.9)	464 (24.4)	832 (28.2)	
1 Jan 1999–15 Jul 1999	89 (16.1)	408 (21.5)	663 (22.5)	
16 Jul 1999–31 Jan 2000	275 (49.8)	465 (24.5)	618 (21.0)	

[1] Data are *n* (%) unless otherwise stated. Less than 2% of data are missing for all characteristics, except for hemoglobin and household income. EBF, exclusive breastfeeding; PBF, predominant breastfeeding; MBF, mixed breastfeeding. "Previous 7 d" refers to breastfeeding practice during the previous 7 d.

[2] *P* value calculated by using a chi-square test across all 3 groups by "previous 7 d" breastfeeding definition.

[3] Mean ± SD (all such values).

[4] *P* value calculated by using a Kruskal-Wallis test across all 3 groups by "previous 7 d" breastfeeding definition.

[5] Calculated by using the method of Capurro et al (13).

[6] Includes breech, forceps, vacuum, and cesarean deliveries.

[7] Midupper arm circumference; method described by Gibson (14).

[8] Primiparous mothers excluded.

[9] Adjusted for inflation.

[10] Median; 25th–75th percentile in parentheses (all such values).

TABLE 3
Exclusive breastfeeding (EBF) rate, incidence of sick clinic visits, and household income according to date of enrollment[1]

	Quartile of enrollment[2]			
	1	2	3	4
Proportion of EBF infants to 6 wk [% (*n*)]				
"Ever since birth" definition[3]	6.9 (1327)	4.6 (1275)	6.3 (1026)	14.1 (1337)
"Previous 7 d" definition[4]	11.4 (1431)	9.4 (1403)	10.1 (1196)	20.8 (1440)
Proportion of EBF infants to 3 mo [% (*n*)]				
"Ever since birth" definition[3]	2.5 (1161)	0.8 (1109)	1.8 (915)	7.8 (1163)
"Previous 7 d" definition[4]	7.3 (1249)	6.1 (1224)	7.4 (1073)	20.6 (1257)
Household income (US$/mo)[5,6]				
Median	82.0	86.9	74.2	74.2
<$1.00/d [% (*n*)]	6.7 (1086)	6.9 (985)	10.4 (937)	12.5 (1131)
Sick clinic visits [no. per 100 child-years (child-years of observation)][6]				
All-cause, 0–6 mo	412.4 (744.6)	328.2 (682.5)	301.0 (576.0)	250.9 (674.5)
Diarrhea-specific, 0–6 mo	26.2 (744.6)	19.9 (682.5)	19.4 (576.0)	10.5 (674.5)
LRTI-specific, 0–6 mo	79.5 (744.6)	59.8 (682.5)	49.3 (576.0)	32.8 (674.5)
All-cause, 0–3 mo	525.9 (374.2)	402.6 (343.2)	400.3 (289.0)	324.9 (338.3)
All-cause, 3–6 mo	297.8 (370.4)	252.9 (339.3)	201.1 (287.0)	176.4 (336.2)
Proportion of all sick clinic visits in children aged 0–6 mo				
At research clinic [% (*n*)]	8.6 (2497)	16.3 (1712)	29.2 (1393)	37.5 (1426)

[1] Tests of general association across the 4 enrollment quartiles: proportions with EBF, household income <$1.00/d, and sick clinic visits at research clinic were tested by using chi-square tests (3 df); median income by using a Kruskal-Wallis test; and incidence of sick clinic visits by using negative binomial regression (3 df Wald test); the result for each test was $P < 0.001$. LRTI, lower respiratory tract infection.

[2] Quartile 1 (25 November 1997–15 June 1998), 2 (16 June 1998–31 December 1998), 3 (1 January 1999–15 July 1999), and 4 (16 July 1999–31 Jan 2000).

[3] Definition refers to all foods consumed since birth.

[4] Definition refers to all foods consumed during the previous 7 d.

[5] Adjusted for inflation.

[6] Based on infants who provided "previous 7 d" breastfeeding information at 3 mo.

for either of these causes (data not shown) and because both are rarely life threatening, our analysis focused on visits for LRTI and diarrhea. Based on the "previous 7 d" data, the visit rate for LRTI was higher in the 43–91-d interval than in the 92–182-d interval (63.5 and 46.4 visits/100 child-year, respectively), whereas the diarrhea-specific visit rate increased with infant age (14.6 and 26.3 visits/100 child-years during the 43–91-d and 92–182-d intervals, respectively). Values for all of these rates were similar when calculated based on infants included in the "ever since birth" feeding definition (Table 4).

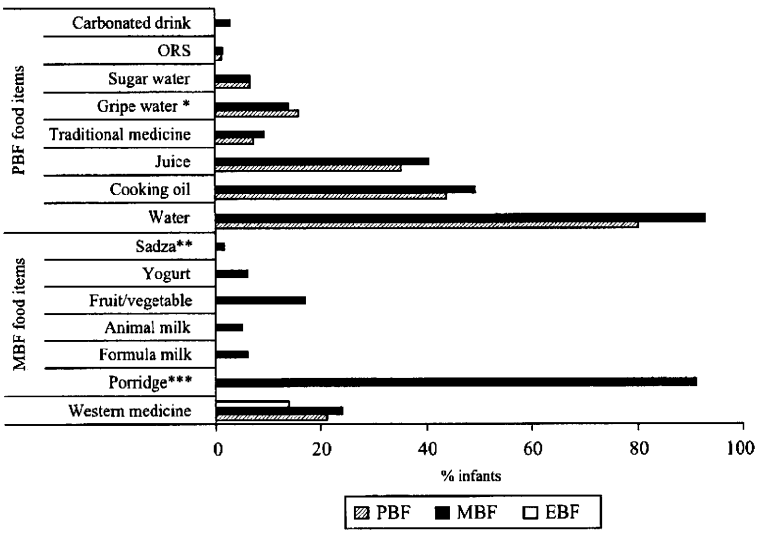

FIGURE 1. Food items consumed by >1% of the infants by breastfeeding practice during the previous 7 d at 3 mo of age. Percentage of infants who had consumed that item. EBF, exclusive breastfeeding ($n = 552$); MBF, mixed breastfeeding ($n = 2946$); PBF, predominantly breastfeeding ($n = 1900$); ORS, oral rehydration solution. *Home remedy for colic and other stomach symptoms. Consists of dill, alcohol, and sodium bicarbonate. **Thickened porridge or dumpling made of maize meal. ***Porridge usually refers to diluted sadza.

TABLE 4
Illness-associated infant clinic visits for all causes, lower respiratory tract infection (LRTI), and diarrhea according to feeding mode between birth and 6 wk or 3 mo according to the "ever since birth" and "previous 7 d" definitions[1]

		Total				LRTI-specific				Diarrhea-specific			
Feeding mode	Days of observation	No. of visits	IRR[2]	95% CI	*P*	No. of visits	IRR[3]	95% CI	*P*	No. of visits	IRR[4]	95% CI	*P*
"Ever since birth"													
43–91-d[5]													
EBF	19,616	155	1.00	—	—	19	1.00	—	—	4	1.00	—	—
PBF	154,856	1531	1.14	(1.93, 1.41)	0.197	267	1.64	(0.88, 3.05)	0.121	72	2.17	(0.70, 6.76)	0.182
MBF	66,686	642	1.11	(0.89, 1.38)	0.366	137	1.91	(0.99, 3.67)	0.052	24	1.73	(0.52, 5.75)	0.371
Total[6]	241,158	2328 (352.9/100 cy)				423 (64.1/100 cy)				100 (15.2/100 cy)			
92–182 d[7]													
EBF	13,369	67	1.00	—	—	9	1.00			1	1.00	—	—
PBF	137,641	900	1.17	(0.85, 1.63)	0.333	169	1.50	(0.58, 3.91)	0.406	101	8.38	(1.07, 65.53)	0.043
MBF	248,607	1656	1.19	(0.86, 1.65)	0.285	333	1.55	(0.60, 3.99)	0.364	192	8.76	(1.13, 68.09)	0.038
Total[6]	399,617	2623 (239.7/100 cy)				511 (46.7/100 cy)				294 (26.9/100 cy)			
"Previous 7 d"													
43–91-d[8]													
EBF	34,872	298	1.00	—	—	46	1.00	—	—	13	1.00	—	—
PBF	169,261	1663	1.08	(0.92, 1.26)	0.347	295	1.24	(0.80, 1.94)	0.336	68	1.03	(0.50, 2.12)	0.942
MBF	61,543	598	1.05	(0.88, –1.25)	0.560	121	1.33	(0.81, 2.19)	0.254	25	1.05	(0.46, 2.39)	0.901
Total[6]	265,676	2559 (351.8/100 cy)				462 (63.5/100 cy)				106 (14.6/100 cy)			
92–182 d[9]													
EBF	49,623	244	1.00	—	—	53	1.00	—	—	16	1.00	—	—
PBF	171,873	1130	1.20	(1.00, 1.44)	0.045	197	0.88	(0.55, 1.43)	0.620	133	2.04	(1.11, 3.77)	0.022
MBF	265,341	1757	1.23	(1.03, 1.46)	0.021	368	1.04	(0.65, 1.65)	0.884	201	2.05	(1.13, 3.72)	0.019
Total[6]	486,837	3131 (234.9/100 cy)				618 (46.4/100 cy)				350 (26.3/100 cy)			

[1] EBF, exclusive breastfeeding; PBF, predominant breastfeeding; MBF, mixed breastfeeding; IRR, incidence rate ratio; cy, child-years. 95% CIs and *P* values calculated by negative binomial regression. "Previous 7 d" refers to breastfeeding practice during the previous 7 d, and "ever since birth" refers to breastfeeding practice since birth.

[2] Adjusted for enrollment date, parity, 5-min APGAR score, and religion.

[3] Adjusted for enrollment, parity, and sex.

[4] Adjusted for enrollment date.

[5] Morbidity by breastfeeding practice at 6 wk ($n = 4965$).

[6] Total incidence rate: sick clinic visits for all causes, LRTI, and diarrhea per 100 cy.

[7] Morbidity by breastfeeding practice at 3 mo ($n = 4425$).

[8] Morbidity by breastfeeding practice at 6 wk ($n = 5470$).

[9] Morbidity by breastfeeding practice at 3 mo ($n = 5398$).

On the basis of the stricter "ever since birth" definition, infants who were predominantly and mixed breastfed before 6 wk of age had, respectively, 1.64 (95% CI: 0.88, 3.05) and 1.91 (95% CI: 0.99, 3.67) times more LRTI-specific clinic visits and 2.17 (95% CI: 0.70, 6.76) and 1.73 (95% CI: 0.52, 5.75) times more diarrhea-specific clinic visits during the subsequent 43–91-d interval than did infants who were exclusively breastfed during the first 42 d of life (Table 4). These differences were not as apparent when the "previous 7 d" definition was used. During the 92–182-d interval, infants who had been predominantly and mixed breastfed during the first 91 d of life made ≈20% more all-cause sick clinic visits based on either feeding group definition, although these differences were statistically significant only on the basis of the "previous 7 d" definition. This higher rate of total visits was primarily driven by diarrhea-specific visits, which were significantly higher based on the "ever since birth" definition (≈8 times) and based on the "previous 7 d" definition (≈2 times) in both the PBF and MBF infants than in the EBF infants. There was no significant difference in LRTI-specific visits between feeding groups based on either feeding definition during the 92–182-d period. A sensitivity analysis, excluding all sick clinic visits that occurred within 7 d from the breastfeeding assessment date, showed that the effect size remained similar (data not shown) and adjustment for vulnerability of the child in the past also did not modify the effect size (data not shown).

DISCUSSION

In this study, early EBF was associated with significantly fewer sick clinic visits than was early PBF or MBF among non-HIV–exposed infants. The magnitude and significance of this association was particularly strong for diarrhea-specific visits.

Several methodologic features of this analysis strengthened our conclusions. First, comparison of subsequent morbidity according to previous breastfeeding practice minimized the effect of reverse causality. Second, we excluded infants who had been fed infant formula soon after birth most likely as a part of neonatal intensive care; inclusion of these infants would likely have overestimated the adverse consequences of MBF. Third, we conducted a sensitivity analysis that excluded sick clinic visits that occurred within 7 d of breastfeeding practice assessment and another analysis that adjusted for infant vulnerability in the past; it was confirmed that the effect size was similar. Fourth, we used 2 breastfeeding definitions that have different strengths and limitations and often correlate poorly (17). Finally, we controlled for the effect of secular trends.

Two mechanisms have been described to explain the protective effects of EBF compared with those of PBF or MBF. First, non–breast milk fluids and foods are often contaminated with pathogens when prepared under unhygienic conditions (18–20), which results in diarrhea and subsequent malnutrition. Second, because breast milk contains a wide array of antiinfective properties, reduced breast milk volume would result in reduced intakes of these factors and leave the infant more vulnerable. Data are quite consistent, demonstrating a displacement effect by formula, animal milk, and solid food (21, 22). However, recent studies indicate that PBF liquids do not result in lower breast milk intake (23, 24). In our study, the deleterious effects of PBF and MBF were of remarkably similar magnitude in all the analyses that we conducted. This finding suggests that the excess diarrhea associated with PBF and MBF was more likely to be due to accompanying pathogens than to a reduced intake of breast milk and its antiinfective factors. Previous studies observed higher morbidity and mortality rates due to diarrhea among MBF infants than among EBF infants but similar rates among PBF infants and EBF infants in Bangladesh (5), in Peru (25), and in a pooled analysis from India, Ghana, and Peru (11). This may be because the food items that shift infants from EBF to PBF and MBF classifications differ depending on the setting. Future studies should examine the particular foods that contribute to PBF and MBF in their communities, as we did in this analysis.

The association between breastfeeding exclusivity and sick clinic visits was more modest for LRTI-specific visits than for visits for diarrhea, reaching marginal significance only among MBF infants during the 43–91-d interval when the "ever since birth" definition was used (IRR: 1.91; 95% CI: 0.99, 3.67; $P = 0.052$). No adverse effect on LRTI associated with either PBF or MBF was observed in the pooled analysis (11), and promotion of EBF was not associated with a reduction in morbidity due to respiratory infections (26). Two previous studies reported a protective effect of EBF compared with MBF on respiratory infections; however, in one of these studies, nonbreastfed infants were included in the MBF group (5), and, in the other study, the periods of morbidity observation and breastfeeding status overlapped completely, so reverse causality may have occurred (25). A possible explanation for the weaker association between EBF and respiratory infections may be that it is mediated by a chain of events where diarrhea is caused by PBF or MBF, which, in turn, gives rise to subsequent malnutrition and susceptibility to respiratory infections.

Several limitations of this study deserve mention. First, because breastfeeding practice was not randomized, the possibility of residual confounding exists because of unmeasured factors. Second, we did not collect data on the frequency or quantity of non–breast milk foods consumed by infants, nor did we collect data on the age at introduction of non–breast milk foods. Therefore, we were unable to estimate whether there is a threshold of nonexclusivity or infant age associated with increased morbidity. Third, our analysis used the breastfeeding practice that preceded the period of observation of outcome as the exposure variable; however, this may have resulted in misclassification of exposure, because the breastfeeding practice preceding the observation period may not necessarily reflect the breastfeeding practice during the period of observation. Finally, most of the clinic visits were conducted in public sector clinics, so we were reliant on nonresearch staff and the mothers themselves for morbidity reports.

The recommendation of exclusive breastfeeding from birth to 6 mo has emerged from the integration of the benefits of exclusive breastfeeding on a wide range of health outcomes, including infant growth, late return of maternal menstruation, and postpartum weight loss (27). Although our study was not intended to assess the optimal duration of exclusive breastfeeding, our study supports and strengthens current recommendations to promote early EBF among all infants. Cluster randomized controlled studies of promotion of exclusive breastfeeding in Mexico (28), India (29), and Belarus (26) found reductions in diarrhea in the intervention group.

Exclusive breastfeeding among HIV-negative Zimbabwean mothers is associated with significant health benefits to their

infants. These findings, together with our earlier observation of reduced postnatal HIV transmission among HIV-exposed infants whose mothers practiced early EBF (9), indicate that universal promotion of EBF is very likely to improve infant health. Our findings are particularly notable because our study was conducted among relatively well-educated urban women, the vast majority of whom had access to tap water, toilet facilities, and electricity.

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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 ≥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 ≥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, ≥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 settings[13] 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 lactation[15] 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 gain[19] 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 ≥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 statiometer, 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 ≥10% weight loss relative to weight at 6 week postpartum in HIV-negative and HIV-positive women, and predictors of ≥10% weight loss in HIV-positive women

K-M methods were used to estimate the cumulative risk of ≥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 ≥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 ≥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 ≥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 ≥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 ≥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)	<0.001
Plasma CD4 (cells/μl)	<350	25	(7.9)	789	(40.5)	<0.001
	≥350	293	(92.1)	1157	(59.5)	
	Median (IQR)*	737	(529–961)	399	(251–559)	<0.001
Plasma HIV-1 RNA (copies/ml)	≤500	—	—	29	(3.4)	
	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)	
	≥25.0	1127	(28.3)	521	(24.0)	
	Median (IQR)*	23.0	(20.9–22.6)	22.6	(20.7–24.9)	<0.001
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
	≥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)	
	≥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 (±7 days) and at least one subsequent weight measurement.
[a]Inflation 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 (±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 ≥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 ±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

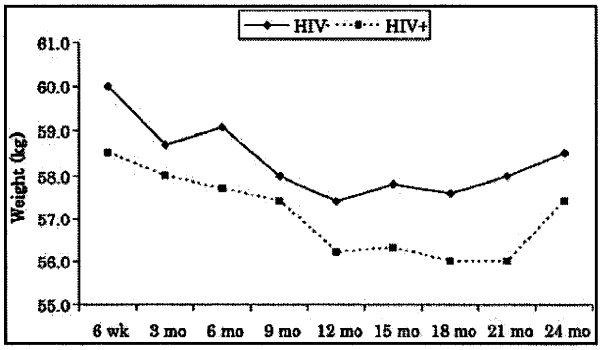

FIG. 1. Median weight at follow-up in HIV-negative and HIV-positive women. Only women who had weight measured at 24 months (within ±7 days of the scheduled visit) and did not become pregnant are included. Only weight measurements conducted within ±7 days of the scheduled follow-up date are included. 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 ≥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 ≥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 ≥10% weight loss was 25% at 457 and 468 days for HIV-positive and HIV-negative women, respectively. Among women who experienced ≥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 ≥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 ≥10% weight loss in HIV-positive women

In univariate analyses, BMI <18.5 at 6 weeks, CD4 <350 cells/μl at delivery, monthly income <US$130, and schooling <7 years were significant predictors of subsequent ≥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 ≥10% weight loss

HIV-positive women who lost ≥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 ≥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 ≥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 ≥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 ≥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 loss[25] 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.

[a]Significantly different from 0 by the Wilcoxon sign rank test ($p < 0.05$).

[b]Median 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 ≥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/μl)	≥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			

[a]Univariate hazards ratio.
[b]Adjusted for baseline CD4 cell count, BMI at 6 weeks, and household income.
[c]Inflation adjusted.
[d]BMI (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, ≥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 eligibility[13] 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 weeks[26] 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 ≥10% WEIGHT LOSS

Mortality	*≥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.
[a]CD4 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 ≥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 ≥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 ≥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.

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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.

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Author Disclosure Statement

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Ⅲ章

Ⅲ章　分担研究報告書

HIV/AIDS予防のため系統的レビューに関する研究

分担研究者　森　臨太郎　東京大学大学院国際保健政策学

研究要旨
本分担班は主に以下の3件の研究を行った。【研究1】系統的レビューに関しては、コクラン HIV・AIDS グループに、途上国および先進国のセックスワーカーのコンドーム使用の行動変容に関するレビューのプロトコールが 2 本出版された。現在フルレビューを投稿中である。【研究2】MSM 感染予防戦略の系統的レビューに関しては、調査が困難であり隠れた対象である Men who have sex with men (MSM)の HIV 調査の方法と HIV 陽性に関連する因子を明らかにすることを目的にレビューを行い、最終的に MSM の HIV の prevalence 調査方法に関する 71 文献、109,833 名の MSM を対象にした調査のメタ回帰分析から、世帯調査および Venue Day Time sampling 法が多く用いられていること、薬物使用が有病率と統計的に優位な関連がみられたることが明らかになった。【研究 3】コクランレビューのタイトルの獲得に関しては、新たに母子感染予防 PMTCT のオーバービューレビューのタイトル“Interventions for preventing mother-to-child HIV transmission: An overview of Cochrane reviews”と行動介入のプロトコール“Structural and community-level interventions for increasing condom use to prevent HIV and other sexually transmitted infections.”を登録し、現在プロトコールを作成投稿中である。
メタ分析では、研究は計画通りに進み、HIV の個別施策層である MSM やセックスワーカーに関する質の高いエビデンスを構築し、国際雑誌に投稿し、国際的な学術の場において意義は大きい。

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A．研究目的

世界的にエイズ対策は大きな転換期にある。本年度の世界エイズ会議では治療から予防へ再び大きな舵がとられ、エイズ治療への傾倒から予防と治療のバランスのとれたエイズ対策に世界の注目が集まっている。しかし予防に関する保健介入には未だ多くの議論があり、理論的分析が必要である。例えば、コンドーム、自発的カウンセリングと検査（VCT)、そして性行為感染症の治療といった伝統的なエイズ予防介入もその効果に関してはさまざまな結果が出ており、人口レベルでの有効性に関しては更なる検討の余地があることが指摘されている。VCT の HIV 陰性被験者に対する効果にしても互いに反駁し合う報告がある。また、男性の包茎手術やセックスパートナー数を減らすための介入など、有効なエビデンスの示されている保健介入に関しては、わが国でもあまり積極的な導入がなされていない。また、わが国のエイズ実証研究は、多くの場

合サンプル数の限られた一時的な横断的聞き取り調査に終始することが多い。それは継続的なコホート研究等の縦断研究を行うためのフィールドが皆無であり、それが欧米と比べてわが国でエイズに関する実証研究を発展させない大きな阻害要因となっている。従ってわが国も危険な行動要因に関するコホート研究や予防や治療の保健介入のランダム化臨床試験を行うための共通基盤であるフィールドを確保し適切な情報システムを導入したうえで、継続的なエイズ研究を行う時期に来ている。

以上を鑑み、本研究は二つの大きな目的を持つ：1）初年度に作成した国内外のエイズ予防に関する保健介入リストに基づき、系統的かつ詳細なメタ分析を行い、最新のエイズ予防に関するエビデンスを提供する。2）コホート研究やランダム化臨床試験を行うための研究フィールドとエイズ保健情報システムを用いて、エイズ予防介入による検査並びに治療への促進・阻害要因を継続的に分析し早期検査並びに早期・継続的治療を進展させる為のエビデンスを発信していく。

この理論的研究と実践的フィールド研究をさらに推進し、我が国よりエイズ予防に関するエビデンスに基づく提言を国内外に対して行う。また、我が国における政策に直結した継続的エイズ理論実証研究を行うための知的・人的貢献の拠点作成も視野に入れ、我が国のエイズ疫学研究において先駆的な役割を果たす。

本分担班では、特に、初年度に作成した国内外のエイズ予防に関する保健介入リストに基づき、系統的かつ詳細なメタ分析を行い、最新のエイズ予防に関するエビデンスを提供することを担当している。

B．研究方法

1．研究体制

東京大学医学系研究科国際保健政策学教室に研究事務局を置いている。研究代表者(渋谷)は1993年よりGlobal Burden of Disease (GBD) プロジェクトに参加して以来保健アウトカム分析を行い続け、2001年から2008年までは同機関において保健プログラムの評価・モニタリング、そして保健システム評価手法の開発と実証分析を行ってきた。エイズ予防保健介入のメタ分析は、英国における根拠に基づくガイドライン作成やコクラン共同計画に参画し、メタ分析の第一人者である森（東大）が担当する。コホート研究等の縦断研究のためのタイ国のフィールドの整備と保健情報システムの構築には野内（複十字病院)、渋谷（東大)、情報分析は、小柳(東大)が行う。エイズ感染症の専門家である医長の本田(国立国際医療センター)は、最新の臨床知見をもとに研究戦略を策定する。エイズ感染症の専門家である堀（聖路加看護大）は、プロジェクトの教育的立場で人材育成を行う。

本分担班は、森が担当し、研究分担者として、堀成美（聖路加看護大学)、研究協力者として大田えりか（財団法人エイズ予防財団）および、Windy Wariki（東京大学大学院医学系研究科・国際保健政策学）の協力を得た。

2．本年度研究

班会議を2回開催し、研究目標および役割分担と連携を確認し、進捗状況の報告と今後の方向性の確認も行った（東京)。

本分担班は主に以下の3件の研究を行った。

【研究１】
コクランレビュー：途上国および先進国のセックスワーカーのコンドーム使用の行動変容に関するレビュー
【研究２】
MSM 感染予防戦略の系統的レビュー
【研究３】
コクランレビューの新たなタイトルの獲得

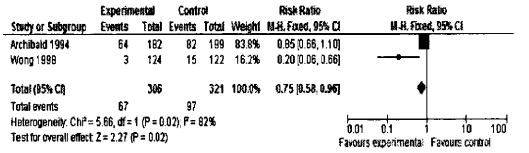
（倫理面への配慮）
研究開始にあたり、データの取り扱いには指針等を順守することとし、個人データなどの取り扱いには十分に注意を払った。

C．研究結果
【研究１】
コクランレビューに関しては、コクランのHIV・AIDS グループのタイトルを２つ登録し、プロトコールを作成し投稿した。HIV のリスクが高いセックスワーカーの行動介入効果のレビューを高所得国と中低所得国に分けて行った。プロトコールは 10 月に以下のように出版された（添付資料 1、2）。
Ota E, Wariki WMV, Hori N, Mori R, Shibuya K. Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in high-income countries. [protocol] *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.:CD006045. DOI: 10.1002/14651858.CD006045.pub2.

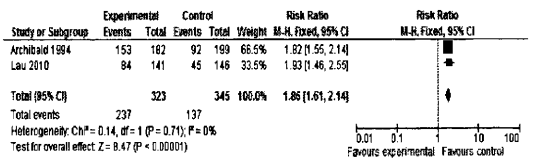
Wariki WMV, Ota E, Hori N, Mori R, Shibuya K. Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in low-income and middle-income countries. [protocol] *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.: CD005272. DOI:10.1002/14651858.CD005272.pub2.

高所得国は、検索された 2655 の文献をスクリーニングし、関連する 34 の研究がみつかった。そのうち内容を詳細に吟味したところ、４つの研究が条件に該当した。低中所得国は、検索された 2655 の文献をスクリーニングし、詳細な吟味の結果、13 の研究が該当しレビューを行った。セックスワーカーの行動介入は、STI 有病率と HIV 感染に関する知識の向上に効果があることを明らかにした。これらの結果をコクランに 11 月に投稿し、現在レビュープロセスにある。

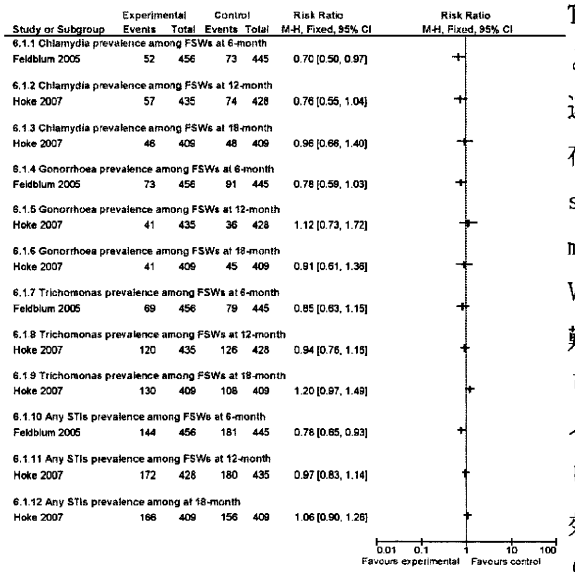
【図 1】高所得国の性感染症罹患



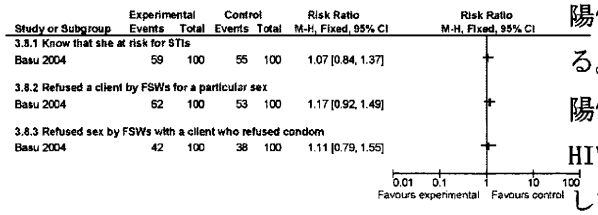
【図 2】高所得国のＨＩＶ感染に関する知識



【図 3】低所得・中所得国のピア教育とクリニックベースカウンセリング vs コンドーム使用のピア教育のみ　18 か月後のＳＴＩ罹患率



【図 4】低所得・中所得国のコミュニティエンパワメント　vs　コンドーム使用にかんする標準ケア



【研究２】

MSM 感染予防戦略の系統的レビューに関しては、調査が困難であり隠れた対象である Men who have sex with men (MSM)の HIV 調査の方法と HIV 陽性に関連する因子を明らかにすることを目的にレビューを行った。Pubmed、Cochrane Library、EMBASE、PsycINFO 等を使用して、網羅的検索を行い、合計 MSM の HIV 調査を検討した論文 2269 ヒット中、重複を除き、現在まで調査されている該当する 188 件の研究についてさらに詳細な検討を行った。最終的に MSM の HIV の prevalence 調査方法に関する 71 文献、109,833 名の MSM を対象にした調査のメタ回帰分析から、世帯調査および Venue Day Time sampling 法が多く用いられていること、薬物使用が有病率と統計的に優位な関連がみられたることが明らかになった。現在、 "A systematic review of HIV surveillance for men who have sex with men" というタイトルで投稿中である。

Venue Day Time sampling 法は、調査が困難である若い MSM を対象とした調査方法として、1996 年ごろから報告されてきた。バイアスは比較的少なく、代表性に優れており、MSM がよく訪れる場所、曜日、時間に、効率的にサンプリングする。手順としては、(1)対象者が集まる場所のマッピング (2) VDT Unit の算出 (3) 参加可能性・対象者のサンプル数などの考慮から、調査対象場所・曜日・時間などの決定 (4) HIV 抗体陽性有病率調査を行う、という 4 段階を経る。日本では MSM の人口レベルの HIV 抗体陽性有病率調査は未だ行われていない。

HIV/AIDS に関する疫学情報は、届出疾患としての報告数と HIV 感染の有無に関して自己報告のインターネット調査、イベントやバーやクリニックなどの施設ベースのサンプリングのみである。基本的な疫学情報がないということは、本当に流行が拡大しているのか、これまで行われてきたＨＩＶ感染予防のための施策が有効であるかどうか評価できない。そのため、このレビューの結果から、日本の沖縄で、MSM の人口レベルの HIV 抗体陽性有病率調査を行うことができないか計画を立案している。予算が確

保でき次第調査を実施したい。
上記の成果の一部は11月に東京で開かれた日本エイズ学会の際に、「日本の流行状況から求められるHIV検査戦略の課題～根拠に基づいた計画とその評価のために何を解決すべきか～」という公開のシンポジウムにて「エビデンスに基づくHIV検査戦略：疫学的視点から」と題して代表の渋谷が発表し、疫学手法を活用したエイズ予防戦略の重要性に関して国内関連機関・団体・研究班との連携と積極的な意見交換を行った。

【研究3】
コクランレビューのタイトルの獲得に関しては、新たに母子感染予防PMTCTのオーバービューレビューのタイトル
“Interventions for preventing mother-to-child HIV transmission: An overview of Cochrane reviews”と行動介入のプロトコール“Structural and community-level interventions for increasing condom use to prevent HIV and other sexually transmitted infections.”（資料3)を登録し、現在プロトコールを作成投稿中である。
“Interventions for preventing mother-to-child HIV transmission: An overview of Cochrane reviews”のオーバービューレビューでは、最近アップデートされた母子感染予防に関する以下の５つのレビューのオーバービューを行う。
1. Interventions for preventing late postnatal mother-to-child transmission of HIV
2. Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women
3. Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection
4. A review on late postnatal antiretroviral interventions for PMTCT
5. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection

D．考察
このように、今年度の３つ目的は、それぞれ達成することができた。また、コクランの次のタイトルを登録することができ、MSMの調査に関しても今後の計画を立案することができた。今後につながる成果がでてきている。
メタ分析では、HIVの個別施策層であるMSMやセックスワーカーに関する質の高いエビデンスを構築し、国際雑誌に投稿し、国際的な学術の場において意義は大きい。また、東京の学会シンポジウムにおいて研究班の取り組む質の高いエビデンスの構築と疫学調査によるモニタリングと評価の重要性に関してより広く啓発できた。

３）今後の展望について
研究終了時に期待される成果は、国内外におけるエイズ予防のための保健介入の効果のエビデンスの構築、継続的なエビデンスの提供とモニタリングと評価の重要性をエイズ予防領域において推進することである。また、エイズ研究においては、「データの収集、評価分析、メタ分析、エビデンス形成、政策提言」といったサイクルを考慮しなければならない。本研究班はそれぞれのサイ

クルの専門家を集結させ、国内外の専門家集団との連携を通じ、知識の共有とネットワークを形成し、我が国における知的・人的貢献のプールを作ることである。
中長期的に期待される成果としては、今後我が国がエイズ予防・治療研究のためのコホート研究や臨床試験を行うためのフィールドを確保・整備し、継続的にエビデンスの提供をしていくためのシステムが確保され、将来的にも我が国の研究者が合同で利用できるような体制を構築する。

E．結論

研究は計画通り順調に進捗しており、成果も現れている。研究が来年度以降も順調に進むことで、国内外におけるエイズ予防のための保健介入の効果のエビデンスの構築、継続的なエビデンスの提供とモニタリングと評価の重要性をエイズ予防領域において推進することができると考えられる。

G．研究発表

1. 論文発表

Ota E, Wariki WMV, Hori N, Mori R, Shibuya K. Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in high-income countries. [protocol] *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.:CD006045. DOI: 10.1002/14651858.CD006045.pub2.

Wariki WMV, Ota E, Hori N, Mori R, Shibuya K. Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in low-income and middle-income countries. [protocol] *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.: CD005272. DOI:10.1002/14651858.CD005272.pub2.

2. 学会発表

渋谷健司. SY8-1 エビデンスに基づくHIV検査戦略:疫学的視点から, 第24回日本エイズ学会シンポジウム8 日本の流行状況から求められるHIV検査戦略の課題～根拠にもとづいた計画とその評価のために何を解決すべきか～.