Weight Changes During and After 6 Months of Breastfeeding in HIV-Infected Mothers Receiving Antiretroviral Therapy in Malawi

Marina Giuliano,¹ Giovanni Guidotti,² Mauro Andreotti,¹ Paola Scarcella,³
Roberta Amici,¹ Haswell Jere,⁴ Jean-Baptiste Sagnon,⁴ Ersilia Buonomo,³
Sandro Mancinelli,³ Maria Cristina Marazzi,⁵ Stefano Vella,¹ and Leonardo Palombi³

EDITOR: Weight changes during breastfeeding are very variable in healthy populations with reported changes during 6 months of lactation between a mean loss of 0.9 kg/month and a mean gain of 0.8 kg/month.¹ Breastfeeding increases the nutrient needs of women, although metabolic adaptations generally occur to protect energy reserves during lactation. In the presence of HIV infection, which also increases metabolic demands, if dietary intake is inadequate, breastfeeding mothers can become nutritionally depleted. Data previously reported on HIV-infected women concerning the potential effect of breastfeeding on maternal weight are controversial with some studies showing no major impact on body weight and adverse outcomes^{2,3} and others reporting significant weight loss and possible associated increased disease progression.^{4–6}

Recently, exclusive breastfeeding up to 6 months postpartum was not reported to be associated with weight loss in HIV-positive women with an intermediate disease stage (CD4⁺ cell count between 200 and 500/mm³), irrespective of baseline body mass index (BMI) and the administration of antiretroviral prophylaxis.⁷

In this study we analyzed weight changes in a cohort of HIV-infected women during and after the breastfeeding period, until 2 years postpartum, and assessed if a difference existed according to immunological stage and the administration of antiretroviral therapy (ART).

Patient population included women enrolled in the SMAC (Safe Milk for African Children) study,⁸ conducted in Malawi between 2008 and 2011, within the DREAM program of the Community of S. Egidio, an Italian faith-based nongovernmental organization. In the study, aimed to assess the safety and pharmacokinetics of ART administration during breastfeeding, ART-naïve women (with no grade 3 or 4 laboratory toxicity and no active tuberculosis) received either zidovudine plus lamivudine and nevirapine (*n* = 126) or stavudine plus lamivudine and nevirapine (*n* = 143) from week 25 of gestation until 6 months postpartum if their CD4⁺

count was >350/mm³ at baseline, or indefinitely if they met the criteria for treatment.

Women were instructed to exclusively breastfeed up to 6 months. At each visit after month 6 information was collected about possible continuation of breastfeeding, and the presence of breast milk was verified by manual breast expression. All women received a monthly nutritional supplementation (including corn flour, rice, beans, peanuts, vegetable oil, and sugar) providing about 500 kcal, 19 g of protein, and 17 g of lipids per person daily for a family of 5. Weight was measured monthly using a mechanical column scale (SECA 711) regularly calibrated on a daily basis. For this analysis all women with available weight data at month 1 postpartum were included. Main outcome measures were the mean weight changes from month 1 during breastfeeding, and over 6-month periods thereafter. The comparisons between the two CD4⁺ groups were performed using general linear models. Statistical analysis was performed using SPSS v. 20.0 (IBM, Somers, NY).

A total of 269 women (mean age 27 years) were studied. At baseline the mean CD4⁺ count was 375/mm³ (47.2% had >350 CD4⁺/mm³) and the mean viral load was 4.2 log₁₀ copies/ml. One month postpartum the mean weight (±SD) was 55.7 kg (±9.3) and the mean BMI was 22.2 (±3.0). During follow-up 30 women (11%) modified their initial regimen either for anemia (eight women replaced zidovudine with stavudine), nevirapine-associated toxicity (18 women replaced nevirapine with lopinavir/r), or severe polyneuropathy/lactic acidosis (four women switched from stavudine to zidovudine). Women breastfed for a median of 180 days (IQR 178–183). In 62 out of 269 women (23%) there was evidence of breastfeeding beyond 6 months. A total of 56/269 (21%) women were exposed to the season of food insecurity (in Malawi between December and March/April)⁹ when infants had the highest breast milk demand (between month 4 and 6 of breastfeeding). There were no differences in the baseline characteristics between the women with baseline CD4⁺ >350/mm³ or <350/mm³ with the exception of age

¹Department of Therapeutic Research and Medicines Evaluation, Istituto Superiore di Sanità, Rome, Italy.

²DREAM Program, Community of S. Egidio, Rome, Italy.

³Department of Biomedicine and Prevention, University of Rome, Tor Vergata, Italy.

⁴DREAM Program, Community of S. Egidio, Blantyre, Malawi.

⁵LUMSA University, Rome, Italy.

(26 vs. 28 years in the two groups, respectively, $p=0.004$, Student's t -test).

During breastfeeding the mean weight change in the entire population from month 1 to month 6 was -1.1 kg (± 3.7). The mean weight loss was significantly higher in women with baseline $CD4^+ > 350/mm^3$ (-1.7 kg ± 4.0) compared to women with baseline $CD4^+ < 350/mm^3$ (-0.6 kg ± 3.3). Between month 6 and month 12 women with a baseline $CD4^+$ count $> 350/mm^3$ gained weight ($+2.28$ kg ± 4.3) and those with a low baseline $CD4^+$ count, who also continued to be on antiretroviral (ARV) treatment, lost weight (-0.23 kg ± 3.7). No other significant difference was observed. The cumulative weight increase between month 1 and month 24 was 1.2 kg ± 5.3 (1.7 kg ± 5.9 and 0.9 kg ± 4.9 in women with baseline $CD4^+ > 350/mm^3$ or $< 350/mm^3$, respectively) (Table 1).

Overall, HIV-infected women in our cohort lost weight during 6 months of breastfeeding. Although the loss was of modest magnitude, it was higher in women with a baseline $CD4^+$ count $> 350/mm^3$; in those with a lower baseline $CD4^+$ count the benefits of ARV therapy in terms of weight gain¹⁰ during the 6 months of breastfeeding were probably stronger than the effects of lactation or, alternatively, women in a more advanced disease stage were maintaining their nutrient reserves making suboptimal breast milk. In the first 6 months after the recommended period of breastfeeding, while women with baseline $CD4^+$ count $> 350/mm^3$ rapidly gained weight, women with lower $CD4^+$ counts continued to lose weight.

Several factors could be involved including unreported continued breastfeeding after 6 months (the inclusion in the general linear model of reported breastfeeding beyond 6 months did not have any effect), the effects of advancing disease on energy expenditure, or the persistence of the effect of breastfeeding on nutritional status for some months after its interruption. Actually, dividing the period between 6 and

12 months in two 3-month periods we observed that in the group with a lower $CD4^+$ count, between 6 and 9 months, the weight change was still negative (mean = -0.25 kg) while between 9 and 12 months the weight started to increase (mean = $+0.20$ kg) (data not shown).

However, after month 12 there was a progressive increase in weight in both groups, and 2 years after delivery in a population of women breastfeeding for 6 months a net weight increase, as compared to month 1, was observed, even in the women with more advanced disease.

Previous studies have addressed this issue. In a substudy of the BAN trial¹¹ (conducted in Malawi on 2,300 women) mothers exclusively breastfeeding until 6 months lost an average of 2.5 kg; however, as opposed to our study, only 35% of these women were on ART (although in the study women on ART lost more weight during breastfeeding than those not provided with antiretroviral drugs), and the weight change was measured from delivery (when the mean BMI was 23.6) and not from 1 month postpartum (including therefore the period when normal physiological changes are expected).

In a different report⁹ of the BAN trial assessing weight changes from 2 weeks postpartum (when the mean BMI was 22.8) to 24 weeks in 1,309 women, maternal ART administration was also associated with weight loss during 6 months of breastfeeding. It was hypothesized that the inclusion in the BAN regimen of lopinavir/ritonavir, frequently associated with diarrhea, may have contributed to the weight loss in these women. In a study conducted in Zambia² 958 women were randomized to breastfeed for a short duration (4 months) or for a duration chosen by themselves (median of 16 months). Overall, women in the long duration group gained less weight from 4 to 24 months compared to those in the short duration group, although the average change in weight from 4 to 24 months postpartum was a net gain rather than a

TABLE 1. WEIGHT (KG) AND BODY MASS INDEX (KG/M²) AT MONTH 1, MONTH 6, AND MONTH 24, AND POSTPARTUM WEIGHT CHANGES (KG) ACCORDING TO BASELINE $CD4^+$ STRATUM

Outcome	All patients		Baseline $CD4^+ > 350/mm^3$		Baseline $CD4^+ < 350/mm^3$		p value ^b
	N ^a	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Month 1							
Weight (kg)	269	55.75 (9.3)	127	55.91 (9.3)	142	55.61 (9.3)	
BMI (kg/m ²)		22.2 (3.0)		22.3 (3.1)		22.2 (2.9)	
Month 6							
Weight (kg)	237	54.68 (9.0)	115	54.30 (9.0)	122	55.17 (9.4)	
BMI (kg/m ²)		21.8 (3.0)		21.6 (3.1)		21.9 (2.8)	
Month 24							
Weight (kg)	188	57.01 (10.8)	70	57.72 (11.3)	118	56.58 (10.4)	
BMI (kg/m ²)		22.8 (3.6)		22.9 (3.1)		22.6 (3.4)	
Weight differences							
Month 1–month 6	237	-1.14 (3.7)	115	-1.73 (4.0)	122	-0.57 (3.3)	0.046
Month 6–month 12	207	0.96 (4.2)	98 ^c	2.28 (4.3)	109	-0.23 (3.7)	< 0.001
Month 12–month 18	193	0.84 (3.5)	81 ^c	1.13 (3.6)	112	0.49 (3.4)	0.069
Month 18–month 24	175	0.75 (3.2)	63 ^c	0.44 (2.6)	112	0.92 (3.5)	0.219
Month 1–Month 24	188	1.23 (5.3)	70 ^c	1.76 (5.9)	118	0.92 (4.9)	0.290

^aNumbers of women with available data at the different time points.

^bp values from all general linear models, adjusted for age, body mass index (BMI) at month 1, and seasonality (exposure to the season of food insecurity); for weight differences between month 6 and month 12 the model was also adjusted for reported breastfeeding after 6 months.

^cWomen with baseline $CD4^+ > 350/mm^3$ interrupted antiretroviral treatment at month 6; those who resumed treatment because of a new pregnancy or because their $CD4^+$ count decreased to $< 350/mm^3$ after month 6 were censored at drug reinitiation.

loss. However, in addition, in that study no ART was administered and the weight change was measured starting from month 4 (when the mean BMI was 21.6), the end of the breastfeeding period for the women in the short duration of breastfeeding group, making the results difficult to compare.

In a randomized trial of breastfeeding versus formula feeding with no ART administration⁶ (conducted in Kenya on 425 women) breastfeeding was associated with a mean weight loss of 0.17 kg per month (similar to what was found in our cohort) and with an increased risk of death (there was a significant relationship between weight loss during follow-up and mortality). However, the latter finding was not confirmed in a subsequent study (conducted in the same country on 300 women), which confirmed that BMI decreased more rapidly in breastfeeding women compared to those not breastfeeding, but showed that mortality did not differ significantly between formula feeders and breastfeeding mothers.⁵ The very low mortality rate of women in our cohort (2.1% 2 years postpartum)⁸ prevented us from assessing any possible difference in subsequent survival, but also suggested no major negative mortality impact.

In the Kesho-Bora trial⁷ conducted in Burkina-Faso, Kenya, and South Africa, HIV-infected pregnant women with CD4⁺ cell counts of 200–500 cells/mm³ were counseled to choose breastfeeding or replacement feeding and randomized to receive perinatal zidovudine and single-dose nevirapine or triple antiretroviral prophylaxis until breastfeeding cessation. Weight changes were assessed in a substudy including 797 women. Overall, mothers' weight remained relatively stable between 2 weeks (when the mean BMI was 24.9) and 6 months postpartum, but ART-treated mothers breastfeeding up to 3 months or up to 6 months lost weight between 2 weeks postpartum and 3 months (–1.1 kg and –0.8 kg, respectively, in line with our findings). Only women with a baseline BMI > 25 who stopped breastfeeding at 3 months had no weight loss, suggesting limited effects only among well-nourished women with a very short duration of breastfeeding.

The limitations of this study include the nutritional supplementation given to all women, which may have mitigated weight loss, and the lack of information on maternal work and household demographics, important determinants of food access.

In conclusion, our study showed that in our cohort HIV-infected women during breastfeeding lost weight, while weight gain occurred after its interruption. Further studies are needed to investigate the weight changes associated with longer periods of breastfeeding, such as the 1-year duration recommended by the last World Health Organization guidelines¹² and the 2-year duration now recommended in Malawi.¹³

Acknowledgments

The authors wish to thank Alessandra Mattei for secretarial support and Marco Mirra and Massimiliano Di Gregorio for informatic assistance.

This work was supported by a grant from the Italian Research Program on AIDS of the Ministry of Health, 2009–2010 (grant 3H/33) and by Esther-Italy, Ministry of Health, 2009–2010 (grant 9M34).

Author Disclosure Statement

Stefano Vella: consultancy (ViiV) and board membership (Gilead, Janssen).

References

- Butte NF and Hopkinson JM: Body composition changes during lactation are highly variable among women. *J Nutr* 1998;128(Suppl):381S–385S.
- Murnane PM, Arpad SM, Sinkala M, *et al.*: Lactation-associated postpartum weight changes among HIV-infected women in Zambia. *Int J Epidemiol* 2010;39:1299–1310.
- Sedgh G, Spiegelman D, Larsen U, *et al.*: Breastfeeding and maternal HIV-1 disease progression and mortality. *AIDS* 2004;18:1043–1049.
- Papathakis PC, Van Loan MD, Rollins NC, *et al.*: Body composition changes during lactation in HIV-infected and HIV-uninfected South African women. *J Acquir Immune Defic Syndr* 2006;43:4467–4474.
- Otieno PA, Brown ER, Mbori-Ngacha DA, *et al.*: HIV-1 disease progression in breast-feeding and formula-feeding mothers: A prospective 2-year comparison of T cell subsets, HIV-1 RNA levels, and mortality. *J Infect Dis* 2007;195:220–229.
- Nduati R, Richardson BA, John G, *et al.*: Effect of breastfeeding on mortality among HIV-1 infected women: A randomised trial. *Lancet* 2001;357:1651–1655.
- Cames C, Cournil A, de Vincenzi I, *et al.*: Postpartum weight change among HIV-infected mothers by antiretroviral prophylaxis and infant feeding modality. *AIDS* 2014;28: 85–94.
- Giuliano M, Andreotti M, Liotta G, *et al.*: Maternal antiretroviral therapy for the prevention of mother-to-child transmission of HIV in Malawi: Maternal and infant outcomes two years after delivery. *PLoS One* 2013;8(7):e68950.
- Widen EM, Bentley ME, Kayira D, *et al.*: Maternal weight loss during exclusive breastfeeding is associated with reduced weight and length gain in daughters of HIV-infected Malawian women. *J Nutr* 2013;143:1168–1175.
- Saghayam S, Kumarasamy N, Cecelia AJ, *et al.*: Weight and body shape changes in a treatment-naïve population after 6 months of nevirapine-based generic highly active antiretroviral therapy in South India. *Clin Infect Dis* 2007;44:295–300.
- Kayira D, Bentley ME, Wiener J, *et al.*: A lipid-based nutrient supplement mitigates weight loss among HIV-infected women in a factorial randomized trial to prevent mother-to-child transmission during exclusive breastfeeding. *Am J Clin Nutr* 2012;95:759–765.
- World Health Organization: 2013. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. Available at www.who.int/hiv/pub/guidelines/arv2013/download/en/index.html.
- Ministry of Health, Malawi: 2011. Clinical management of HIV in children and adults. Available at www.hivunitmohmw.org.

Address correspondence to:

Marina Giuliano
Department of Therapeutic Research and
Medicines Evaluation
Istituto Superiore di Sanità
Viale Regina Elena 299
00161 Rome
Italy

E-mail: marina.giuliano@iss.it