Food Insufficiency Is Associated With Lack of Sustained Viral Suppression Among HIV-Infected Pregnant and Breastfeeding Ugandan Women

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Abstract: Food insecurity is associated with poor virologic outcomes, but this has not been studied during pregnancy and breastfeeding. We assessed sustained viral suppression from 8 weeks on antiretroviral therapy to 48 weeks postpartum among 171 pregnant and breastfeeding Ugandan women; 74.9% experienced food insufficiency. In multivariable analysis, food insufficiency [adjusted odds ratio (aOR) 0.38, 95% confidence interval (CI): 0.16 to 0.91], higher pretreatment HIV-1 RNA (aOR 0.55 per 10-fold increase, 95% CI: 0.37 to 0.82), and lopinavir/ritonavir versus efavirenz (aOR 0.49, 95% CI: 0.24 to 0.96) were associated with lower odds of sustained viral suppression. Interventions to address food security may improve virologic outcomes among HIV-infected women.

Key Words: food insecurity, nutrition, perinatal transmission, pregnancy, household hunger, virologic outcomes

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INTRODUCTION

Food insecurity, defined as uncertain access to safe and nutritious foods,[1] and food insufficiency (FI), in which inadequate quantities of food are available,[2–4] have been associated with poor health outcomes in HIV-infected populations, including reduced adherence to antiretroviral therapy (ART) and mortality.[5–7] Moreover, food insecurity has been associated with lower rates of viral suppression among HIV-infected adults in the United States[8–10] and rural Uganda.[11]

Pregnant and breastfeeding women may be particularly vulnerable to food insecurity and insufficiency because of increased nutritional demands[12,13] at a time of reduced physical ability to generate income and obtain and prepare food.[14] Poor nutritional status and food insecurity have been associated with adverse pregnancy outcomes among HIV-infected women and reduced uptake of interventions to prevent perinatal transmission.[15–19] Among pregnant women treated with combination ART, food insecurity has been associated with reduced pharmacokinetic exposure to antiretrovirals (ARVs), inadequate maternal weight gain during pregnancy, low birth weight, and preterm delivery.[20–22] Furthermore, food insecurity may also be a barrier to exclusive breastfeeding.[23,24]

World Health Organization guidelines now recommend that all pregnant and breastfeeding HIV-infected women initiate combination ART and encourage lifelong therapy.[25] Achieving and maintaining viral suppression during pregnancy and breastfeeding will be critical to attaining the dual

goals of preserving maternal health and eliminating perinatal HIV infections. Viral suppression, in turn, is dependent on adequate ARV adherence and pharmacokinetic exposure, both of which may be influenced by insufficient food intake.[6,7,20,26–28]

Although food insecurity and insufficiency may be major drivers of virologic outcomes among childbearing HIV-infected women in resource-limited settings, this relationship has not yet been examined. In Uganda, where the prevalence of HIV is 7.3%[29] and 48% of households are food energy deficient,[30] food security and sufficiency may impact HIV outcomes. Therefore, we examined the association between household FI and viral suppression during pregnancy and breastfeeding in a cohort of HIV-infected women in rural Uganda.

METHODS

Study Design and Population

We performed a secondary analysis of data from the PROMOTE-Pregnant Women and Infants study (NCT00993031), which was designed to test the hypothesis that lopinavir/ritonavir would reduce the prevalence of placental malaria. Study procedures[31] and results[20–22,24,31–35] are described elsewhere. Briefly, the study enrolled HIV-infected, ART-naive pregnant women between 12 and 28 weeks gestation in Tororo, Uganda from December 2009 to September 2012. Women initiated ART at enrollment and were randomized to receive lopinavir/ritonavir or efavirenz, in combination with lamivudine/zidovudine. Participants received multivitamins containing iron and folic acid, iron supplements, mebendazole, and trimethoprim/sulfamethoxazole prophylaxis. Women were seen at the study clinic every 4 weeks; participants continued ART and were followed for up to 1 year postpartum. Women were counseled to breastfeed their infants for 1 year, with exclusive breastfeeding for the first 6 months of life. One participant switched from lopinavir/ritonavir to efavirenz because of the need for tuberculosis treatment; all other participants remained on their assigned study drug.

This analysis includes women who participated in assessments of food security, which were performed among all participants actively enrolled from September 11, 2011, to February 4, 2012. The study protocol was approved by the Makerere University School of Medicine Research and Ethics Committee, the Uganda National Council for Science and Technology, Cornell University Institutional Review Board, and the University of California, San Francisco Committee on Human Research. Participants provided written informed consent in their preferred language.

Measurements

HIV-1 RNA was measured at screening, 8 weeks after ART initiation, delivery, 8, 24, and 48 weeks postpartum, and at other intervals for clinical management. HIV-1 RNA polymerase chain reaction testing was performed using COBAS AMPLICOR version 1.5 (Roche Molecular Diagnostics, Pleasanton, CA) until September 2012, and thereafter with the *m*2000 RealTi*m*e HIV-1 assay (Abbott Laboratories, Abbott Park, IL). The primary outcome for this analysis was sustained viral suppression from 8 weeks after ART initiation to 48 weeks postpartum. Viral suppression was dichotomized as "sustained" if HIV-1 RNA $\leq$400 copies per milliliter (the lower limit of detection of the assays) at all measured time points and "not sustained" if HIV-1 RNA $>$400 copies per milliliter at any measured time point. Sixteen participants had missing HIV-1 RNA measurements at 8 weeks on ART (N = 8) or 48 weeks postpartum (N = 8).

FI was operationalized using the Household Hunger Scale (HHS),[36] a subset of 3 questions about insufficient food quantities from the 9-item Household Food Insecurity Access Scale,[37] which has been previously been validated for cross-cultural use[38] and measured among HIV-infected adults in rural Uganda.[28,39] The HHS asks the frequency over the previous 4 weeks of (1) having no food to eat of any kind in one's household, (2) going to sleep at night hungry, and (3) going a whole day and whole night without eating. A response of "never" received 0 points, "rarely or sometimes" received 1 point, and "often" received 2 points; points were summed as a score, with a maximum score of 6 points for a response of "often" to all 3 questions. For logistic regression analyses, FI was dichotomized as no household hunger (HH) versus any HH (any positive response, indicating the presence of FI). FI was assessed once, in the season when food is most abundant in Tororo, such that FI scores would be the most conservative and have the least seasonal variation. FI interviews were conducted among 197 women, at a median of 5.6 months postpartum (interquartile range 2.2–9.2); 18 participants were interviewed before delivery.

A household wealth index was generated by performing a principal component analysis of questions regarding household possession of assets, including a radio, telephone, television, motorcycle, or bicycle, among all PROMOTE participants.[22] The first principal component was used to create the index. Tertiles of the wealth index were used to categorize individual household wealth relative to the cohort. Participants in the middle and highest tertiles of wealth were grouped together for comparison with those in the lowest wealth tertile. Residence within the town of Tororo was defined as urban based on GPS coordinates; other residences in Tororo district were classified as rural. Gestational age at enrollment was determined based on last menstrual period and fetal ultrasound.[21] For calculation of body mass index (BMI), maternal height was measured using a wall-mounted measuring tape (Seca 206; Seca, Hamburg, Germany); maternal weight was measured using a Seca 876 mechanical scale until September 2011 and thereafter using a Seca 874 digital scale. Participants were asked whether they were breastfeeding every 4 weeks postpartum. The end of breastfeeding was defined as the last period in which a participant reported any breastfeeding (exclusive or partial). ART adherence was assessed by self-reported recall of the number of pills taken of the expected number of pills over the 3 days before each study visit.

Statistical Analysis

Characteristics of enrolled participants with and without FI were compared using the χ^2 test or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for

continuous variables. The proportion of participants with and without FI who achieved viral suppression at individual time points was evaluated using Fisher's exact test because of the small number of participants who did not achieve viral suppression at each time point. A 4-week measurement window was used for virologic outcomes.

Logistic regression models were used to evaluate the association between sustained viral suppression, FI, and covariates in our causal model (see Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/A755). We postulated that the association between FI and sustained viral suppression is mediated through effects on adherence, absorption/pharmacokinetics/bioavailability, BMI, depression, poor nutrition, and reduced protein binding of drug. ART regimen and pretreatment HIV-1 RNA were included in the multivariable model as independent predictors of sustained viral suppression. Household wealth was included in the model as a confounder of the relationship between FI and viral suppression. Age was evaluated as a potential confounder. Using the causal model as a guide, we evaluated the effect of individual predictors and confounders, and assessed overall model fit to achieve the final model. Inclusion of age in the multivariable model did not alter the association between FI and viral suppression and did not improve overall model fit; thus, age was excluded from the final model. Statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC).

RESULTS

Participant Characteristics by Food Insufficiency Status

Of 197 women in the PROMOTE study who underwent FI assessment, 26 were excluded from this analysis: 2 did not deliver, 8 were withdrawn before 48 weeks postpartum, and 16 had missing HIV-1 RNA measurements. There were no statistically significant differences between included and excluded participants in any predictor variables, including FI status and pretreatment HIV-1 RNA, and viral suppression at delivery. Among 171 participants, 43 (25.1%) reported no FI (score 0) and 128 (74.9%) reported FI (any HH) (Table 1). Of 128 participants with FI, 12 (9.4%) reported severe HH (score 4–6), 70 (54.7%) reported moderate HH (score 2–3), and 46 (35.9%) had little HH (score 1). At baseline, characteristics were similar between participants with and without FI, including maternal age, gestational age, CD4 cell count, and $\log_{10}$ HIV-1 RNA. At 24 weeks postpartum, 99.2% of food insufficient participants and 100% of food sufficient participants were breastfeeding their infants; 68.6% (food insufficient) and 80.5% (food sufficient) reported exclusive breastfeeding. At 48 weeks postpartum, 91.7% of food insufficient participants and 95.1% of food-sufficient participants reported partial breastfeeding. Two infants acquired HIV; both of their mothers reported FI (one moderate and one severe HH).

Virologic Outcomes

Overall, a high proportion of participants achieved viral suppression at individual time points throughout the study

TABLE 1. Characteristics of 171 HIV-Infected Pregnant Women in the PROMOTE Trial at Enrollment and During Study Follow-Up, by Food Insufficiency Status

	Food Insufficiency	
Characteristics	**Any (N = 128)**	**None (N = 43)**
Enrollment		
Age, mean (SD), yrs	29.4 (5.6)	29.3 (5.3)
Education completed, n (%)		
Less than primary	14 (10.9)	8 (18.6)
Primary or higher	114 (89.1)	35 (81.4)
Household wealth, n (%)		
Lowest	50 (39.7)	11 (25.6)
Middle/highest	76 (60.3)	32 (74.4)
Urban residence (versus rural), n (%)	20 (16.0)	10 (24.4)
No. previous pregnancies, n (%)		
0	9 (7.0)	5 (9.8)
1–2	29 (22.7)	11 (25.6)
3 or more	90 (70.3)	27 (62.8)
No. living children, median (IQR)	3.0 (1.5–4.0)	3.0 (1.0–5.0)
Gestational age, median (IQR), wk	20.1 (17.7–24.5)	22.1 (17.4–24.4)
BMI, median (IQR), kg/m^2	21.1 (19.9–22.9)	21.9 (20.4–24.1)
HIV diagnosed in current pregnancy, n (%)	54 (42.2)	17 (39.6)
WHO stage 1, n (%)	123 (96.1)	42 (97.7)
CD4 cell count, median (IQR), $cells/mm^3$	386 (271–487)	423 (261–559)
Pretreatment HIV-1 RNA, median (IQR), $\log_{10}$ copies/mL	4.3 (3.4–4.9)	4.2 (3.5–4.8)
During Study Follow-Up		
Efavirenz-based ART regimen (versus lopinavir/ritonavir), n (%)	68 (53.1)	18 (41.9)
Self-reported ART adherence, mean (SD), %		
During pregnancy	97.2 (8.8)	99.1 (3.0)
During breastfeeding	99.2 (2.4)	99.6 (1.5)
During pregnancy and breastfeeding	98.8 (2.5)	99.5 (1.6)
Grade 1 or 2 nausea or vomiting during pregnancy or breastfeeding, n (%)	45 (35.2)	14 (32.6)
Grade 1 or 2 diarrhea during pregnancy or breastfeeding, n (%)	64 (50.0)	13 (30.2)*
Breastfeeding, n/N (%)		
24 wk postpartum, partial or exclusive	119/120 (99.2)	41/41 (100)
24 wk postpartum, exclusive	83/121 (68.6)	33/41 (80.5)
48 wk postpartum, partial	110/120 (91.7)	39/41 (95.1)
Viral suppression, n/N (%)		
8 wk after ART initiation	111/128 (86.9)	42/43 (97.7)
Delivery	109/121 (90.1)	37/40 (92.5)
8 wk postpartum	110/124 (88.7)	36/40 (90.0)
24 wk postpartum	101/116 (87.1)	40/40 (100)
48 wk postpartum	112/128 (87.5)	41/43 (95.4)
Sustained viral suppression, n/N (%)†	77/128 (60.2)	34/43 (79.1)‡

*$P = 0.02$.
†At all measured time points from 8 weeks after ART initiation to 48 weeks postpartum.
‡$P = 0.03$.
IQR, interquartile range; WHO, World Health Organization.

(Table 1); 90.1% of food insufficient women and 92.5% of food sufficient women were virologically suppressed at delivery. A total of 77 women (60.2%) with FI achieved sustained viral suppression, compared with 79.1% of women reporting no FI ($P = 0.03$). The proportion of participants who achieved sustained viral suppression by HH status was 34 of 43 (79.1%, no HH), 29 of 46 (63%, little HH), 39 of 70 (55.7%, moderate HH), and 9 of 12 (75%, severe HH).

In a multivariable model of sustained viral suppression, FI [adjusted odds ratio (aOR) 0.38, 95% confidence interval (CI): 0.16 to 0.91, $P = 0.03$], pretreatment HIV-1 RNA (aOR 0.55 per 10-fold increase, 95% CI: 0.37 to 0.82, $P < 0.01$), and ART regimen of lopinavir/ritonavir versus efavirenz (aOR 0.49, 95% CI: 0.24 to 0.96, $P = 0.04$) were associated with lower odds of viral suppression (Table 2).

DISCUSSION

In this cohort of HIV-infected women in rural Uganda who initiated ART during pregnancy, FI was highly prevalent, consistent with previous estimates among nonpregnant HIV-infected Ugandan adults.[11] Although the proportion of women who achieved viral suppression was high overall in this cohort, with more than 90% virologically suppressed at delivery,[33] FI was associated with 62% lower odds of achieving and sustaining viral suppression during pregnancy and breastfeeding. To our knowledge, this is the first study to evaluate the association between FI and virologic outcomes during pregnancy and breastfeeding, when viral suppression has implications both for preserving maternal health and reducing the risk of perinatal transmission. Thus, in this cohort of women with high median CD4 cell count, the strong association between FI and lack of sustained viral suppression suggests that FI may be an important and modifiable risk factor for virologic failure.

The results of this study are consistent with previously published reports of poor virologic outcomes among nonpregnant food insecure individuals in the United States and Uganda, in whom food insecurity was associated with 40%–77% lower odds of viral suppression.[8–11] The consistency of these findings across diverse settings and the modifiable nature of food insecurity underscore the need to understand the mechanisms by which FI and food insecurity may lead to virologic failure, such that appropriate interventions can be implemented. Potential causal pathways include behavioral[7] (eg, decreased adherence due to lack of food with which to take medicines, competing resource demands precluding access to medicines), psychological[6,40] (eg, depression and anxiety associated with FI, leading to decreased adherence), and pharmacokinetic alterations[26] (eg, altered ARV absorption and reduced bioavailability in food insecure individuals).

Nutritional supplements, ready to use supplementary foods, and other strategies may reduce FI and are increasingly being studied and implemented programmatically in nonpregnant HIV-infected populations.[41–43] In a pilot study in Zambia, food supplementation led to increased ART adherence.[44] Similarly, food supplementation was associated with improved clinic attendance, BMI, and food security in Haiti.[45] Another study in Haiti that randomized nonpregnant HIV-infected adults on ART to ready to use supplementary foods or a corn-soy blend supplement found similar improvements in CD4 cell count, ART adherence, and household wealth index in each arm.[46] Nonetheless, the optimal components, quantity, and duration of supplementation are not yet known.[43,47,48]

Whereas several studies have addressed micronutrient (vitamin/mineral) supplementation among HIV-infected pregnant women,[49] few studies of macronutrient (carbohydrate/protein/fat) supplementation have been conducted in this population, such that little is known about the impact on viral suppression. A trial in Malawi found that a lipid-based nutrient supplement plus maize reduced weight loss during breastfeeding among HIV-infected women compared with those receiving a maize provision alone, but did not affect infant weight gain.[50,51] The first study of macronutrient supplementation among HIV-infected pregnant women (a subgroup of PROMOTE participants not included in this analysis) found that a lipid-based nutrient supplement and instant soy porridge were highly acceptable.[48]

This study has several important strengths, including being the first to investigate the role of FI in virologic outcomes among pregnant and lactating women and the repeated measures of HIV-1 RNA. A limitation of this study

TABLE 2. Factors Associated With Sustained Viral Suppression From 8 Weeks After ART Initiation to 48 Weeks Postpartum, Among 171 HIV-Infected Pregnant and Breastfeeding Women in the PROMOTE Trial

Variable	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Food insufficiency				
Any household hunger versus none	0.40 (0.18 to 0.90)	0.03	0.38 (0.16 to 0.91)	0.03
Pretreatment HIV-1 RNA				
Per 10-fold increase	0.55 (0.38 to 0.82)	<0.01	0.55 (0.37 to 0.82)	<0.01
ART regimen				
Lopinavir/ritonavir versus efavirenz	0.59 (0.31 to 1.11)	0.10	0.49 (0.24 to 0.96)	0.04
Household wealth				
Lowest versus middle/highest	0.69 (0.36 to 1.32)	0.26	0.76 (0.38 to 1.53)	0.45
Age				
Per year	1.06 (1.00 to 1.12)	0.06		

OR, odds ratio.

is that FI was measured only once, and the HHS only assessed experiences in the 4 weeks before FI interviews. In addition, FI was generally not measured at the beginning of the period during which virologic outcomes were measured. Thus, it is possible that variation in FI occurred throughout the study period that we were unable to measure. Repeated measurements of FI would have provided stronger evidence of causality. However, because FI was measured in the season of greatest food security (ie, when FI is lowest in Tororo), the strength of the relationship between FI and viral suppression may be underestimated. Participants received resources that are protective against some of the potential pathways by which FI may be deleterious (ie, reimbursement for transportation to the study clinic, free provision of ART and medical care); this may have also attenuated the strength of the observed association between FI and virologic outcomes. In addition, we do not have data on quantity or quality of diet.

In summary, FI may be an important and modifiable determinant of adverse virologic outcomes among pregnant and lactating women. As millions of HIV-infected women worldwide initiate and continue ART during pregnancy and breastfeeding, there is a pressing need to address barriers to achieving and maintaining viral suppression. Interventions to reduce FI may result in improved health outcomes among HIV-infected women and their children and merit further attention from the research and programmatic communities. Future research should elucidate the mechanisms driving this association, such that efficacious and cost-effective interventions can be implemented.

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