HIV-Exposed, Uninfected Infants in Uganda Experience Poorer Growth and Body Composition Trajectories than HIV-Unexposed Infants

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Background: HIV-uninfected infants of HIV-positive women may experience worse growth and health outcomes than infants of HIV-negative women, but this has not been thoroughly investigated under the World Health Organization's most recent recommendations to reduce vertical transmission.

Objective: To determine whether HIV-exposed and -uninfected (HEU) infants whose mothers received Option B+ have higher odds of experiencing suboptimal growth trajectories than HIV-unexposed, -uninfected infants, and if this relationship is affected by food insecurity.

Design: Repeated anthropometric measures were taken on 238 infants (HEU = 86) at 1 week and 1, 3, 6, 9, and 12 months after delivery in Gulu, Uganda. Latent class growth mixture modeling was used to develop trajectories for length-for-age z-scores, weight-for-length z-scores, mid-upper arm circumference, sum of skinfolds, and arm fat area. Multinomial logistic models were also built to predict odds of trajectory class membership, controlling for socioeconomic factors.

Results: HEU infants had greater odds of being in the shortest 2 length-for-age z-scores trajectory classes [odds ratio (OR) = 3.80 (1.22–11.82), OR = 8.72 (1.80–42.09)] and higher odds of being in smallest sum of skinfolds trajectory class [OR = 3.85 (1.39–10.59)] vs. unexposed infants. Among HEU infants, increasing food insecurity was associated with lower odds of being in the lowest sum of skinfolds class [OR = 0.86 (0.76–0.98)].

Conclusions: There continues to be differences in growth patterns by HIV-exposure under the new set of World Health Organization guidelines for the prevention of mother-to-child transmission of HIV and the feeding of HEU infants in low-resource settings that are not readily identified through traditional mixed-effects modeling. Food insecurity was not associated with class membership, but differentially affected adiposity by HIV-exposure status.

Key Words: HIV-exposed and -uninfected, anthropometry, HAZ, LAZ, sum of skinfolds, MUAC

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INTRODUCTION

HIV-exposed, uninfected (HEU) infants may be at increased risk of a number of adverse outcomes. Although their health has been shown to be markedly better than those living with HIV, there is evidence to suggest that, before widespread antiretroviral therapy (ART), HEU infants experienced worse growth and increased risk of morbidity and mortality compared with their HIV-unexposed counterparts.[1–9]

HEU infants may also be at increased risk of experiencing the negative consequences of food insecurity. This is both because HIV is often associated with increased food insecurity,[10] and food insecurity is associated with myriad adverse outcomes.[11,12] These include worse maternal body composition, exclusivity of breastfeeding, perceived breast milk quality and quantity, and maternal stress.[13–15]

Over the last decade, the World Health Organization (WHO) has made several changes to its recommendations for the prevention of mother-to-child transmission (MTCT) of HIV and the feeding of HEU infants in low-resource settings. Since 2012, the WHO recommends Option B+: universal, lifelong, ART for all HIV-positive pregnant or breastfeeding women.[16] It further recommends that HEU infants in low-resource settings be exclusively breastfed for 6 months and that breastfeeding continues for at least 1 year.[17] The effects of intrauterine exposure to HIV and ART on infant birth outcomes and subsequent growth remain unknown; however, studies indicate potentially harmful impacts of the virus and/or medicines.[1,18–22]

The reasons for the historically worse growth of HEU infants are not known. Some have posited environmental exposures after delivery,[1,2,7,9,23–25] others suggest molecular metabolic abnormalities since conception,[18,26,27] or even alterations in the microbiome.[28] However, because the current recommendations have only been recently adopted, it is unclear whether Option B+ or recommendations for prolonged breastfeeding have been successful in eliminating the differences between HEU and HIV-unexposed and -uninfected (HUU) infants in health and wellbeing.

To our knowledge, 3 studies to date have considered the growth trajectories of HEU infants under the new guidelines. They suggest that growth differences persist, but conclusions are limited given their divergent methodologies. For example, HEU infants in Kigali, Rwanda participating in a study of Option B+ and breastfeeding for up to 2 years had low length-for-age and slightly elevated weight-for-length.[29] However, this study did not include HUU comparator infants; comparisons were relative to the WHO standard throughout the first 2 years of life. Two studies have used mixed-effects modeling to contrast the growth patterns of HEU infants treated under current WHO recommendations to comparable HUU infants. One study showed that HEU infants in urban Nigeria were at higher risk of stunting and underweight than comparable HUU infants.[30] The second, in South Africa, found that HEU infants had slower linear growth than their HIV-unexposed counterparts.[31] However, body composition measures such as skinfold assessments, mid-upper arm circumference (MUAC), or arm fat area (AFA) were not taken in either study, and analyses were limited to longitudinal, multilevel regression modeling. Regression-based longitudinal approaches assume that there is a single, typical growth pattern for the entire population. However, if the underlying biological mechanisms and risk factors act differently within subgroups of a population, for example within HIV-exposed and -unexposed infants, the assumption of a single underlying distribution can be problematic.[32,33]

Therefore, to better understand differences in growth patterns between HEU and HUU infants, we first compared length-for-age z-scores (LAZs), weight-for-length z-scores (WLZs), MUAC, sum of skinfolds, and AFA among otherwise comparable HEU and HUU infants in northern Uganda. To examine heterogeneity in growth patterns, we used latent class growth mixture modeling to identify infants' growth trajectories. Latent class growth mixture modeling (sometimes shortened to "trajectory modeling") is a statistical approach to classifying outcomes based on their patterns across time. Trajectory modeling is more flexible than traditional longitudinal modeling because it allows for the identification of subgroups whose curves can take on different shapes, rather than being forced to remain parallel, as in traditional regression analyses.[33] Here, we use trajectory modeling to group infants with similar growth patterns into what are called "classes." With the creation of classes, the mean growth patterns of each class can be graphically represented and predictors of class membership can be determined using regression techniques.

We hypothesized that, relative to HUU infants, HEU infants would be at increased risk of belonging to classes that experienced poor growth trajectories for LAZ, WLZ, MUAC, sum of skinfolds, and AFA. We further hypothesized that greater food insecurity would be related to increased risk of belonging to classes that experienced poor growth.

METHODS

The Postnatal Nutrition and Psychosocial Health Outcomes Study (PostNAPS) took place at the Gulu Regional Referral Hospital (GRRH) in Gulu, Uganda from October 2012 to January 2015. PostNAPS is the follow-on to PreNAPS, a longitudinal study that examined the relationships between food insecurity, psychosocial health, and nutritional status during pregnancy and postpartum (clinicaltrials.gov NCT02922829 and NCT02925429).

Details on study procedures and ART are described elsewhere.[34–37] Briefly, women (n = 403) were invited to enroll in the Prenatal Nutrition and Psychosocial Health Outcomes Study (PreNAPS) if they were seeking care at GRRH, had a gestational age between 10 and 26 weeks (assessed using last menstrual period), lived within 30 km of the hospital, and knew their HIV status. HIV-infected women were oversampled from the general population with a ratio of 2 to 1 (HIV-uninfected: HIV-infected), such that the prevalence of HIV among women in this study is higher than the general population. In accordance with Ugandan national policy, all women at the GRRH received free antenatal care and medications. In addition, upon presenting at the antenatal care clinic, HIV-positive women received ART and sulfamethoxazole trimethoprim (Septrin; Aspen Pharmacare, Durban, South Africa).

At the PreNAPS enrollment visit, demographic data including last menstrual period, education, marital status, urban/rural residency, age, and previous displacement (because of the 20-year protracted civil war), were collected. A household asset index was derived using principal components analysis from the self-report of household assets based on the Ugandan National Panel Survey 2009/2010,[14] with higher scores indicating greater wealth. Food insecurity data were collected using the 9-item Individual Food Insecurity Access Scale[36] during all prenatal and postnatal visits (range: 0–27); higher scores indicate greater food insecurity. We used the food insecurity score from the last prenatal visit as it is most likely to reflect food security status throughout the study period. Exclusive breastfeeding at 1 week, 3, and 6 months was determined through a series of questions about breastfeeding and receipt of nonhuman milk foods since the last visit, and scored as binary (yes/no).

Visits were conducted at 1 week and 1, 3, 6, 9, and 12 months postpartum. Maternal height, weight, MUAC, and waist circumference were taken at all postpartum visits. Infant weight, length, MUAC, and head circumference were taken at enrollment and all subsequent visits. Infant skinfold data collection for all infants began at one month postpartum. Trained research staff collected anthropometric measures in duplicate; if there was substantial difference in the first 2 measurements, a third measure was collected. Weight was collected using a digital scale (Seca 874; Seca North America, Chio, CA), height/length using a wall-mounted stadiometer and recumbent boards (Seca 206/Seca 417; Seca North America), and MUAC using a nonstretchable, retractable tape measure. Subscapular, triceps, suprailiac, and mid-thigh skinfold thickness measures were obtained on the right side of the body using Harpenden calipers (Baty International, Burgess Hill, United Kingdom).

All 246 PreNAPS participants who delivered singleton births after May 9, 2013 were eligible and agreed to participate in PostNAPS (see Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/B498). Birthweight data were collected at enrollment, and infant body composition assessments were collected at enrollment in July 2013; repeat skinfold and AFA measures were available for 234 infants. Eight infants were dropped because they had less than 2 visits or were missing baseline data, resulting in an analytic sample of 238 infants (86 HEU and 152 HUU).

At baseline, 51 HIV-infected women had not received HIV medicines and initiated ART with a regimen of tenofovir, lamivudine, and evfavirenz (TDF/3TC/EFV). Of the 35 women who were diagnosed before the index pregnancy, 11 reported taking azidothymidine, 26 received nevirapine, 2 reported 3 TC, and 1 reported highly active antiretroviral therapy. One woman reported receiving a second-line treatment. Infants received 480 mg of Septrin daily until HIV results were confirmed to be negative; HEU infants also received nevirapine daily for the first 6 months of life.

The institutional review boards (IRBs) at Cornell University and Gulu University approved the study procedures for PreNAPS. These 2 IRBs and the IRB at Weill Cornell Medical College approved PostNAPS procedures. Permission to conduct the study in Uganda was granted by the Ugandan National Council for Science and Technology. All mothers provided written informed consent for both PreNAPS and PostNAPS.

Statistical Analysis

LAZ and WLZ were calculated using the WHO igrowup macro in R.[38] Basic descriptives were then calculated and *t* tests were used to compare values between HIV-exposed and -unexposed infants.

Latent trajectories were developed for LAZ, WLZ, MUAC, sum of skinfolds, and AFA using the lcmm package in R.[39] Trajectory modeling groups individuals by the development of a certain outcome over time.[33] In contrast to traditional approaches to growth modeling, which assume that all infants come from the same underlying distribution and that growth curves are simply shifted from one another, this approach allows for growth curves of subpopulations or "classes" to take on fundamentally different shapes. Therefore, with this approach, we can investigate not only whether HEU infants and HUU infants experience different growth at particular time points, but if their growth curves have different shapes. Trajectory models require only specification of the expected relationship between the outcome and time.[33] Three types of time relationships (in this case, infant age) were considered in the development of growth trajectories: age and age^2 terms with a linear link, age and age^2 terms with a spline link, and age with a spline link (with 4 equidistant knots). Models specifying 2–7 classes were considered. Because of limited variation at younger ages, a log transformation was applied to MUAC and AFA values.

We only considered models in which no class contained less than 9% of the population because we wanted classes to actually represent groups of infants rather than isolate one or 2 infants as different. Among these models, we chose those with the best fit as measured by Baysian information criterion (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B498). For all measures, the age and age^2 spline models had the best fit. Infants were assigned to the latent class to which they had the highest probability of belonging for each growth parameter.

Mean growth trajectories for each class were then plotted in R using the ggplot2 package.[40] To understand how these growth parameters were interrelated, the relationship between class membership in any 2 of the anthropometric measures (LAZ, WLZ, MUAC, sum of skinfolds, and AFA) was examined using analysis of variance.

Multinomial logistic regressions were used to consider the relationship between odds of growth trajectory class membership and HIV status and food insecurity, and maternal education, height, age, employment, previous maternal displacement, infant sex, season of birth, asset index, gestational age, and exclusive breastfeeding to 3 months.[41] The breastfeeding status of 6 infants was unknown at 3 months and they were dropped from analytic sample for multinomial logistic regression; no other values for covariates were missing. An interaction term was included between food security and HIV status to allow for the relationship between food security and odds of class membership to vary by HIV exposure status. The class that contained the most infants was used as the referent to increase power.

Finally, to compare the trajectory modeling approach with traditional regression, we used the lme4 package in R to conduct a mixed-effects longitudinal analysis in a *post-hoc* analysis.[42] We examined the relationships between the same set of independent variables and LAZ and sum of skinfolds only, because these were the 2 growth trajectories for which HIV-exposure was statistically significant.

RESULTS

A total of 238 infants had baseline data and at least 2 repeated, simultaneous length and weight measures (see Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/B498). The mean number of study visits was

TABLE 1. Characteristics of Mother–Infant Dyads in PostNAPS Included in Analytic Sample, by Maternal HIV Status (n = 238)

	HIV+ Mother	HIV− Mother	*P* Comparing ± Mothers
N	36%*	64%	
Infant			
Female sex	43%	47%	0.59
Born in hungry season (February-May)	30%	38%	0.26
Gestational age	39.14 (2.4)	39.44 (2.3)	0.36
Infant anthropometrics			
Breastfeeding			
EBF at baseline	83%	72%	**0.02**
EBF at 3 mo	59%	42%	**0.03**
EBF at 6 mo	17%	8%	0.08
Birthweight, kg	3.4 (5.0)	3.4 (4.8)	0.63
LAZ at 1 mo	−0.7 (1.3)	−0.1 (1.1)	**<0.001**
LAZ at 9.5 mo	−0.8 (1.1)	−0.5 (1.1)	0.05
WLZ at 1 mo	0.6 (1.3)	0.3 (1.3)	0.15
WLZ at 9.5 mo	0.3 (1.2)	0.1 (1.2)	0.24
MUAC at 1 mo	11.8 (1.0)	11.9 (1.0)	0.26
MUAC at 9.5 mo	14.1 (1.2)	14.0 (1.3)	0.68
Sum of skinfolds at 1 mo (cm)	29.2 (8.1)	30.4 (7.5)	**0.02**
Sum of skinfolds at 9.5 mo (cm)	38.0 (8.6)	38.9 (7.6)	0.99
AFA at 1 mo	1444.8 (215.6)	1437.0 (195.6)	0.80
AFA at 9.5 mo	1640.8 (285.7)	1627.5 (307.6)	0.47
Maternal			
Age, y	25.8 (5.6)	24.9 (5.2)	0.19
Education beyond primary school	38%	51%	0.06
Height, cm	162.6 (5.8)	162.6 (6.2)	0.97
BMI at first prenatal visit	22.9 (3.1)	22.9 (2.9)	0.88
Asset score	−0.3 (1.4)	0.2 (1.6)	**0.02**
Household food insecurity access score	6.8 (5.4)	5.2 (4.1)	**0.01**
Was displaced	55%	53%	0.77
Mother is not formally employed	50%	45%	0.44

Presented as percent and mean. SDs are included in parentheses for continuous values.
Bold reflects *P*-value < 0.05.
*This percentage reflects the percent of the whole whereas the other percentages are calculated as the percent within each exposure category.

5.77. Mothers of HEU infants reported lower asset and higher food insecurity scores (Table 1). Food insecurity scores were generally consistent over the study period, with mean values ranging from a high of 6.47 at the first postnatal visit to a low of 5.43 at the last visit. There was no statistically significant difference in the mean values of the food insecurity scores reported at the last prenatal visit or any of the subsequent visits (analysis of variance *P* = 0.212). HEU infants were more likely to be exclusively breastfed at 1 week and 3 months postpartum, but this difference was no longer significant at 6 months.

In cross-sectional descriptive analyses at one month of age, HEU infants were somewhat shorter and thinner than HUU infants (Table 1). HEU infants had mean LAZ that were −0.54 units shorter for their age and sex than unexposed infants, and had sum of skinfold measures that averaged 1.2 cm smaller. HEU infants were significantly shorter over the whole period (Fig. 1).

Four latent growth trajectories for LAZ and WLZ, and 3 latent growth trajectories emerged for MUAC, sum of skinfolds, and AFA (Fig. 2). Sum of skinfold and AFA-class membership were significantly associated with LAZ and WLZ-class membership (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/B498). For example, infants in the middle classes for sum of skinfolds and AFA tended to be in the tall-mid class for LAZ and the middle WLZ-class. Infants in the low AFA class tended to be in the short-mid LAZ-class and the low or rapidly falling WLZ-classes.

HEU infants had higher odds of belonging to LAZ-classes that experienced suboptimal growth than HUU infants (Fig. 2 and Table 2). In the final multivariate models, HEU infants had higher odds than HUU infants of being in either of the 2 shortest trajectory classes than the second tallest class, the referent (Table 2).

Among the 234 infants with repeated skinfold measures, HEU infants also tended to have worse patterns in the growth of their sum of skinfold measures than HUU infants (Fig. 2). HEU infants had increased odds of being in the thinnest class of sum of skinfolds; 44% of infants in the lowest sum of skinfolds class

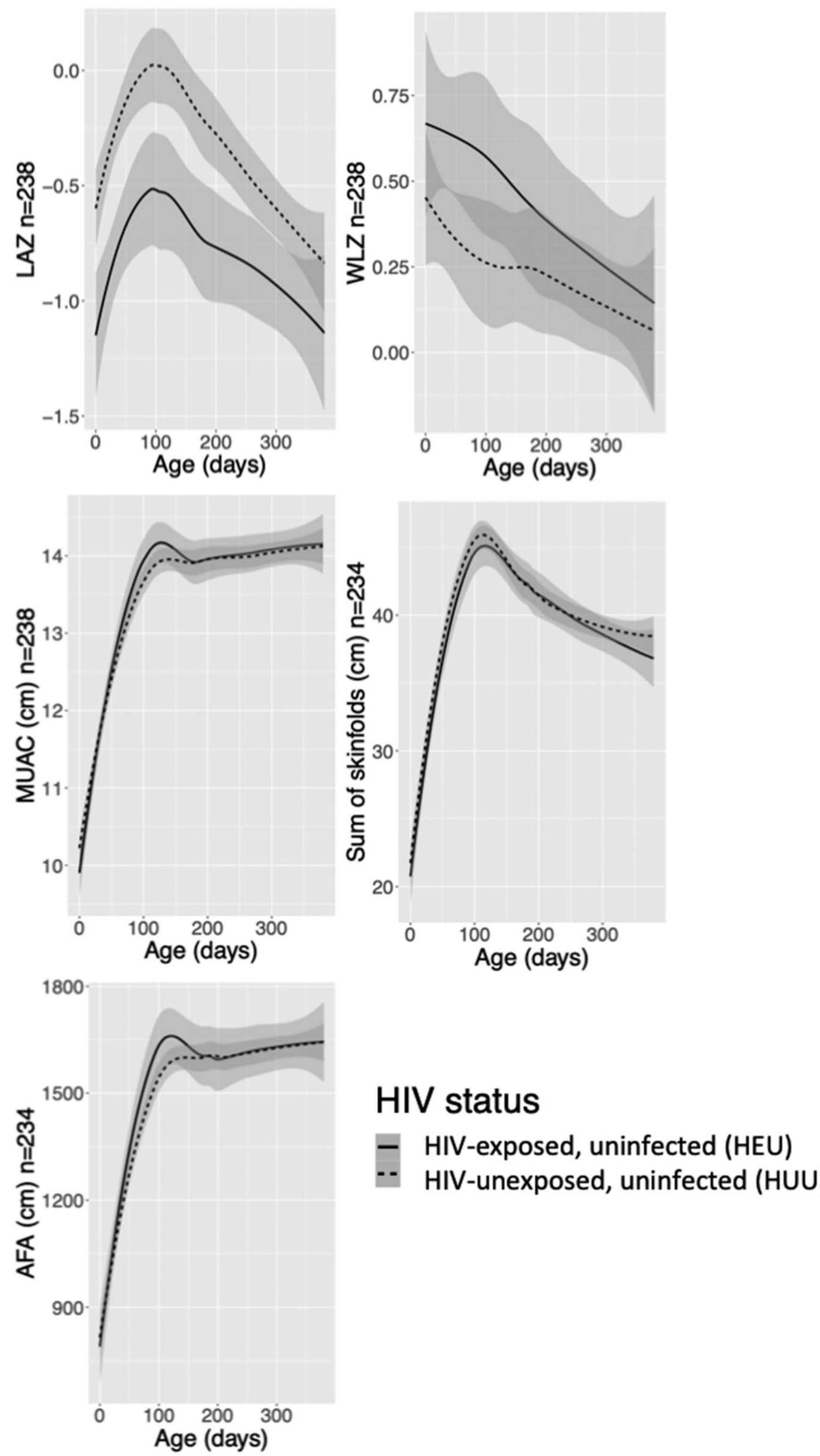

FIGURE 1. Growth trajectories of HEU and HUU infants. HEU infants have lower mean LAZ through the first year of life; however, there are no differences in WLZ, MUAC, sum of skin folds, or AFA between HEU and HUU infants.

were HEU (Table 3). Although latent growth trajectories were developed for WLZ, MUAC, and AFA, there was no difference in odds of class membership by exposure status (see Tables 3–5, Supplemental Digital Content, http://links.lww.com/QAI/B498).

To see how results differed by analytic technique, we used mixed-effects regression to analyze the 2 growth parameters which significantly differed by HIV-exposure status, LAZ, and sum of skinfolds. In this analysis, HEU infants were shorter than

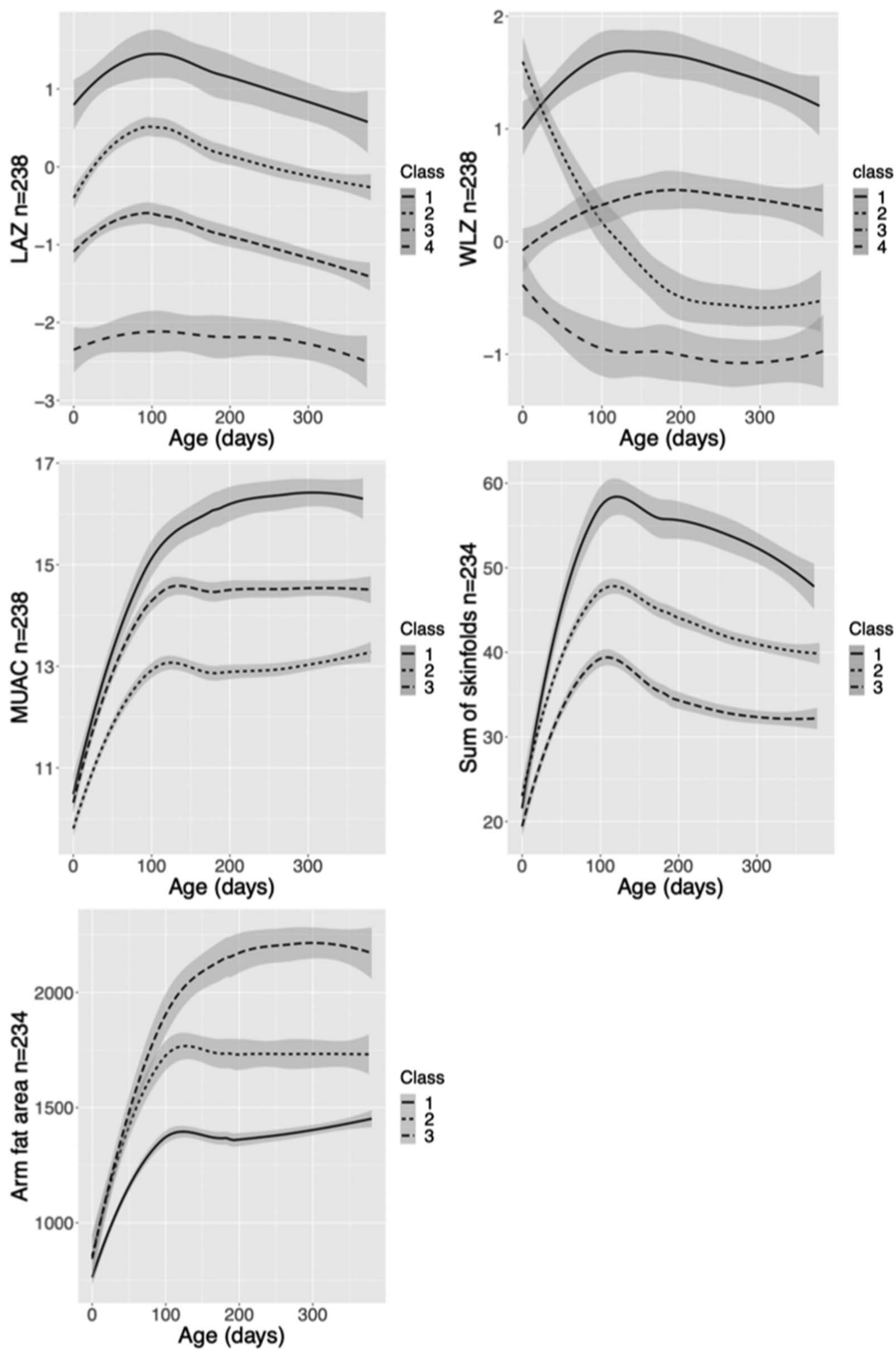

FIGURE 2. Mean growth trends of trajectory classes by anthropometric measure indicate that some subgroups experience fundamental differences in the shapes of their growth over time.

HUU infants (consistent with what we found in trajectory models), but there was no longer a difference in sum of skinfolds.

There were no significant relationships between food insecurity and trajectory membership. However, among HEU infants, greater food insecurity was associated with lower

TABLE 2. HEU Infants Have Increased Odds of Being in the Shortest 2 LAZ Classes in Logistic Regressions

	Class 1		Class 2		Class 3		Class 4	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
N = 232	Tallest		Mid-Tall		Mid-Short		Shortest	
Univariate analysis considering exposure status alone	0.475	0.48 to 0.15	Ref		1.522	0.82 to 2.83	**2.710**	**0.23** to **1.76**
Multivariate analysis								
Maternal HIV	0.769	0.77 to 0.11	Ref		**3.802**	**1.22 to 11.82**	**8.717**	**1.80 to 42.09**
Food insecurity score	1.022	1.02 to 0.88	Ref		0.976	0.88 to 1.08	1.105	0.96 to 1.28
FS × maternal HIV	0.955	0.96 to 0.76	Ref		0.886	0.76 to 1.03	0.845	0.70 to 1.02
Mother completed more than primary school	1.885	1.89 to 0.61	Ref		0.588	0.29 to 1.19	0.432	0.17 to 1.14
Maternal height	0.989	0.99 to 0.91	Ref		**0.904**	**0.85 to 0.96**	**0.839**	**0.77 to 0.92**
Female infant	0.726	0.73 to 0.27	Ref		0.597	0.31 to 1.16	**0.329**	**0.13 to 0.84**
Maternal age	1.005	1.00 to 0.90	Ref		0.965	0.90 to 1.03	0.973	0.90 to 1.06
Previous maternal displacement	0.493	0.49 to 0.17	Ref		1.427	0.63 to 3.25	0.868	0.31 to 2.46
Mother is not formally employed	0.910	0.91 to 0.30	Ref		1.116	0.54 to 2.29	1.054	0.39 to 2.83
Asset index	1.279	1.28 to 0.96	Ref		1.071	0.85 to 1.35	1.113	0.79 to 1.57
Gestational age	1.266	1.27 to 0.95	Ref		0.881	0.75 to 1.03	**0.739**	**0.62 to 0.90**
EBF to 3 mo	1.485	1.48 to 0.54	Ref		1.038	0.53 to 2.05	1.414	0.57 to 3.54
Born in the hungry season (February-May)	0.575	0.58 to 0.19	Ref		0.798	0.39 to 1.62	1.335	0.52 to 3.42

	Class 1		Class 2		Class 3		Class 4	
Descriptives	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%*
N = 238†	23		101		77		37	
Maternal HIV	4	17%	31	31%	**31**	**40%**	**20**	**54%**
Food insecurity score	4.7	4.2	6.0	4.5	5.1	4.6	**7.1**	**5.5**
Mother completed more than primary school	16	70%	52	51%	31	40%	12	32%
Maternal height	164.0	6.7	164.5	6.3	**161.2**	**4.8**	**159.6**	**5.3**
Female infant	11	48%	53	52%	33	43%	**11**	**30%**
Maternal age	25.3	5.7	26.0	5.5	24.6	4.8	24.5	6.1
Previous maternal displacement	14	61%	77	76%	61	79%	27	73%
Mother is not formally employed	9	39%	45	45%	38	49%	19	51%
Asset index	0.9	2.4	0.0	1.5	0.0	1.5	−0.3	1.1
Gestational age	40.4	1.7	39.7	2.1	39.1	2.4	38.2	2.8
EBF to 3 mo	11	48%	45	45%	37	48%	23	62%
Born in the hungry season (February-May)	6	26%	37	37%	26	34%	14	38%

Bold reflects P-value < 0.05.
*Percentages are calculated within classes, not between. That is, 70% of kids in class 1 have mothers who completed more than primary school.
†6 infants were dropped from the multinomial logistic regression due to missing values regarding breastfeeding status.
CI, confidence interval; OR, odds ratio.

odds of being in the lowest sum of skinfolds class [odds ratio interaction = 0.86 (0.76–0.98)] (Table 3).

DISCUSSION

In this cohort of HUU and HEU Ugandan infants whose mothers received Option B+, trajectory modeling revealed important differences in outcomes for LAZ and sum of skinfolds that would have otherwise been obscured using basic descriptive statistics or traditional regression models.

In simple cross-sectional comparisons between HEU and HUU at one month, HEU infants had lower LAZ and smaller sum of skinfolds than HUU infants, and these differences dissipated by 9.5 months (Table 1).

However, using latent class growth mixture modeling, HEU infants had higher odds of belonging to the 2 shortest LAZ-classes (Table 2) and belonging to the lowest sum of skinfolds class (Table 3) compared with HUU infants across time. In other words, HEU infants consistently experienced growth challenges in both length and adiposity. When we investigated differences in growth patterns using the more conventional longitudinal, mixed-effects regression models, HEU infants also experienced statistically significantly worse growth outcomes in LAZ compared with HUU (β = −0.62, see Table 6, Supplemental Digital Content, http://links.lww.com/QAI/B498). However, differences were not seen for sum of skinfolds.

TABLE 3. HEU Infants Have Increased Odds of Being in the Lowest Sum of Skinfold Class in Logistic Regressions

	Class 1		Class 2		Class 3	
	OR	95% CI	OR	95% CI	OR	95% CI
N = 230	High		Mid		Low	
Univariate analysis considering exposure status alone	1.908	0.79 to 4.57	Ref		**1.895**	**1.07 to 3.35**
Multivariate analysis			Ref			
Maternal HIV	3.793	0.84 to 17.28	Ref		**3.854**	**1.39 to 10.59**
Food insecurity score	1.071	0.92 to 1.25	Ref		1.085	0.99 to 1.19
FS × maternal HIV	0.882	0.73 to 1.07	Ref		**0.857**	**0.76 to 0.98**
Mother completed more than primary school	0.710	0.27 to 1.87	Ref		0.637	0.34 to 1.20
Maternal height	0.965	0.90 to 1.04	Ref		0.999	0.95 to 1.04
Female infant	0.454	0.18 to 1.17	Ref		0.786	0.44 to 1.42
Maternal age	1.015	0.92 to 1.12	Ref		1.039	0.98 to 1.11
Previous maternal displacement	0.878	0.29 to 2.66	Ref		0.610	0.30 to 1.25
Mother is not formally employed	2.476	0.89 to 6.89	Ref		**2.008**	**1.03 to 3.90**
Asset index	1.127	0.84 to 1.51	Ref		0.951	0.77 to 1.17
Gestational age	1.006	0.83 to 1.23	Ref		1.010	0.90 to 1.14
EBF to 3 mo	0.712	0.28 to 1.82	Ref		1.176	0.64 to 2.16
Born in the hungry season (February-May)	0.485	0.18 to 1.34	Ref		**0.471**	**0.22 to 1.00**
Descriptive	**Mean/N**	**SD/%**	**Mean/N**	**SD/%**	**Mean/N**	**SD/%***
N = 234†	25		120		89	
Maternal HIV	11	44%	35	29%	**39**	**44%**
Food insecurity score	5.7	4.3	5.5	4.6	**6.1**	**4.8**
Mother completed more than primary school	11	44%	64	53%	35	39%
Maternal height	161	6	163	6	163	6
Female infant	8	32%	59	49%	39	44%
Maternal age	25	6	25	5	26	6
Previous maternal displacement	19	76%	94	78%	65	73%
Mother is not formally employed	15	60%	48	40%	**46**	**52%**
Asset index	0.3	1.2	0.2	1.8	−0.1	1.4
Gestational age	39.4	2.0	39.4	2.4	39.3	2.3
EBF to 3 mo	11	44%	55	46%	50	56%
Born in the hungry season (February-May)	7	28%	48	40%	**24**	**27%**

Bold reflects P-value < 0.05.
*Percentages are calculated within classes, not between. That is, 44% of kids in class 1 have mothers who completed more than primary school.
†6 infants were dropped from the multinomial logistic regression due to missing values regarding breastfeeding status.
CI, confidence interval; OR, odds ratio.

This suggests that there are important differences in the shapes of growth curves that neither cross-sectional analyses nor traditional longitudinal models with their strong set of assumptions can capture.

Not only do HEU infants have a higher tendency to be in low LAZ and sum of skinfolds trajectory classes, but there is an association between sum of skinfolds class and LAZ class, indicating that it is the same infants that tend to be small in both of these measures (P-value < 0.01, see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/B498). Although it is possible that this relationship simply reflects that shorter infants are also smaller in their skinfold measurements, the (nonsignificantly) larger WLZ of HEU infants compared with HUU infants at one month suggests that HEU infants are gaining weight at the expected rate relative to their size. Therefore, their subsequent smaller skinfold measures likely indicate differences in the pattern of adipose deposition. Although it may be tempting to dismiss these differences as not meaningful because z-scores become more similar over time, there is extensive evidence that early growth patterns are associated with long-term health risks, even if subsequent catch-up growth is achieved.[43,44]

These altered growth patterns (shorter infants with less subcutaneous fat) suggest that biological mechanisms to conserve nutrient stores may be occurring in HEU infants either in response to ART or the virus itself. Data are not available to investigate possible hormonal or immunological explanations of these mechanisms, but we encourage their exploration in future research by collecting data on acute phase proteins and other immunological factors.

Thus, to our first hypothesis, we found differences in growth patterns related to HIV-exposure under the new set of WHO guidelines for the prevention of MTCT of HIV and the feeding of HEU infants in low-resource settings. Because we controlled for socioeconomic factors, breastfeeding, and gestational age, we believe the most plausible explanation for the differences in growth is a biological effect of HIV and/or ART. Nonetheless, we are unable to make causal claims. Furthermore, we did not find significant differences in MUAC, WLZ, or AFA. It is possible that this is because the underlying mechanisms that affect sum of skinfolds and LAZ are not acting the same way on these measures. More likely, their higher variation, the rapid fluctuation of some indicators (eg, WLZ), and our small sample sizes simply prevented the identification of these effects. In contrast, length is a well-established indicator of long-term nutritional status.[45]

To our second hypothesis, that greater food insecurity would be associated with poor growth, we found that maternal food insecurity itself did not predict trajectory membership. However, regarding sum of skinfolds among HEU infants, we found a significant interaction between food insecurity and HIV exposure, such that greater food insecurity was related to *decreased* odds of being in the lowest class (Table 3). Although this could be interpreted to indicate that food insecurity is protective against being in the lowest class, it likely reflects the significantly increased odds of being in this class already experienced by HEU infants because of their exposure status, that is, food insecurity simply cannot further increase these odds.

Most of the covariates associated with suboptimal growth were consistent with previous literature. For example, greater maternal height and female sex were related to lower odds of being in the 2 shortest classes (Table 2). This is consistent with our understanding of drivers of child height and with another study of HEU infants in the era of Option B+ in Rwanda.[29] Data from the Rwandan and Ugandan DHS also show less severe growth deficits in female infants than males.[46,47]

This study has many strengths, including repeated diverse anthropometric measures among comparable groups of HEU and HUU infants. To our knowledge, this is the most detailed comparison of growth in HEU and HUU infants in the same setting, in duration of follow-up, and types and frequency of anthropometric assessments. However, sample size limitations could result in low power and the failure to identify some true associations, for example, with WLZ, MUAC, or AFA. In addition, because this is an observational study, there may be residual confounding because of socioeconomic characteristics, other behavioral differences, or the direct biological effect of HIV and/or ART exposure. However, differences in breastfeeding rates are not likely to have caused these differences in outcomes because breastfeeding is accounted for in the models.

In conclusion, HEU infants in northern Uganda on Option B+ experienced worse growth patterns in LAZ and sum of skinfolds than their unexposed counterparts in the first year of life. Food insecurity was not associated with class membership, but differentially affected adiposity by HIV-exposure status. Although enormous strides have been made to support the health and wellbeing of HEU infants and their mothers, these data suggest the need to focus on the gap between the growth of HEU and HUU infants. More information is needed about the drivers of these differences, including physiological and pharmacologic influences, to support the health and wellbeing of the growing population of HEU children in sub-Saharan Africa.

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