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Body Composition Trajectories During the First 23 Months of Life Differ by HIV Exposure Among Infants in Western Kenya: A Prospective Study

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A B S T R A C T

Background: Infants who are HIV-exposed and uninfected have suboptimal growth patterns compared to those who are HIV-unexposed and uninfected. However, little is known about how these patterns persist beyond 1 year of life.

Objectives: This study aimed to examine whether infant body composition and growth trajectories differed by HIV exposure during the first 2 years of life among Kenyan infants using advanced growth modeling.

Methods: Repeated infant body composition and growth measurements (mean: 6; range: 2–7) were obtained from 6 weeks to 23 months in the Pith Moromo cohort in Western Kenya (n = 295, 50% HIV-exposed and uninfected, 50% male). Body composition trajectory groups were fitted using latent class mixed modeling (LCMM) and associations between HIV exposure and growth trajectories were examined using logistic regression analysis.

Results: All infants exhibited poor growth. However, HIV-exposed infants generally grew suboptimally than unexposed infants. Across all body composition models except for the sum of skinfolds, HIV-exposed infants had a higher likelihood of belonging to the suboptimal growth groups identified by LCMM than the HIV-unexposed infants. Notably, HIV-exposed infants were 3.3 times more likely (95% CI: 1.5–7.4) to belong to the length-for-age *z*-score growth class that remained at a *z*-score of ≤ -2, indicating stunted growth. HIV-exposed infants were also 2.6 times more likely (95% CI: 1.2–5.4) to belong to the weight-for-length-for-age *z*-score growth class that remained between 0 and −1, and were 4.2 times more likely (95% CI: 1.9–9.3) to belong to the weight-for-age *z*-score growth class that indicated poor weight gain besides stunted linear growth.

Conclusions: In a cohort of Kenyan infants, HIV-exposed infants grew suboptimally compared to HIV-unexposed infants beyond 1 year of age. These growth patterns and longer-term effects should be further investigated to support the ongoing efforts to reduce early-life HIV exposure-related health disparities.

Keywords: HIV-exposed uninfected, food insecurity, infant growth, body composition, WHO *z*-scores, nutritional epidemiology, infant growth epidemiology, infant growth trajectories, Western Kenya

Abbreviations used: ART, antiretroviral therapy; HCAZ, head circumference-for-age z-score; LAZ, length-for-age *z*-score; LCMM, latent class mixed modeling; MUAC, middle-upper arm circumference; WAZ, weight-for-age *z*-score; WLZ, weight-for-length *z*-score.

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Introduction

The health of HIV-exposed and uninfected infants improved after antiretroviral therapy (ART) became widely available to pregnant women living with HIV. As a result, fewer infants now become infected with HIV during pregnancy or postnatally [1, 2]. The WHO recommends lifelong ART "Option B+" [3] for all pregnant or lactating individuals, although it has been suggested that exposure to ART or HIV in utero affects subsequent growth [2, 4–7]. HIV-exposed infants grow suboptimally [8–11] and are at an increased risk for cognitive and motor delays early in life compared to their HIV-unexposed and uninfected counterparts [12–14].

It has been suggested that HIV-exposed and uninfected infants may grow suboptimally due to congenital metabolic differences [4, 15, 16]. Individuals living with HIV also face a greater risk of experiencing food insecurity [17, 18] and suboptimal body composition during pregnancy and postpartum, which may lead to in utero growth deficits that persist through the first year of life [19, 20]. Moreover, infants exposed to ART during pregnancy have shown growth deficits in utero, resulting in worse growth patterns early in life (e.g., the first year of life), although the longer-term effects on growth are not well understood [5]. However, the relationships between HIV exposure and measurements of growth or body composition over time have not been assessed to compare HIV-exposed and unexposed infants using advanced growth modeling in infants beyond 1 year of age.

Determinants of growth over time are typically evaluated using traditional longitudinal regression models. A shortcoming of this approach is that it assumes that the sample is derived from 1 population and does not allow for flexible examinations of growth patterns and their predictors [21]. Latent class mixture modeling (LCMM) can be used to identify and examine subgroups whose trajectories of growth curves follow different shapes when there is heterogeneity in growth patterns [22]. This methodology is advantageous because it is data driven and identifies underlying trajectory patterns rather than relying on externally imposed grouping criteria. It also provides a visual representation of distinguishable growth or body composition patterns and allows for the examination of predictors of these overall patterns.

It has been previously established that in utero exposure to HIV and ART is associated with poor growth outcomes in infants and children. Therefore, we sought to examine the associations between these prenatal factors with growth and body composition among infants and toddlers using the advanced growth modeling package LCMM. To our knowledge, this is the first evaluation of the body composition and growth among HIV- and ART-exposed and unexposed infants through the first and second years of life using this latent class analysis approach. As an exploratory analysis, we also examined the modifiable and nonmodifiable predictors of body composition and growth, such as maternal food insecurity. We hypothesized that HIV exposure and higher food insecurity would be associated with suboptimal growth parameters, as determined using LCMM.

Methods

Study subjects

Data were taken from the Pith Moromo 2 study, a cohort designed to study the health consequences of food and nutrition insecurity during pregnancy and lactation. This clinical trial was registered at clinicaltrials.gov as NCT02974972. The study was conducted at 7 family AIDS care and educational services clinics in rural and urban Nyanza, Kenya, between 2014 and 2017. At these clinics, women living with HIV could receive Option B+ ART and other HIV health services. Women were eligible to participate in the study if they were $\geq$18 years of age, were pregnant for $\leq$30 weeks, had a known HIV status, and were not planning to move from the study area. Participants were purposively sampled across various food insecurity and HIV statuses (i.e., negative, newly diagnosed (i.e., index pregnancy), and known positive).

A total of 371 pregnant women were enrolled and mother-infant dyads were followed up until 21 months postpartum. In-person visits were scheduled at 6 and 8 months of gestation. Two surveys were conducted by telephone at 1 week and 6 months postpartum, while in-person study visits with mothers and infants were scheduled when the child was ~1.5, 3, 9, 12, 15, 18, and 21 months old. Most visits were scheduled around the planned measurement time; however, the last planned visit was held at a mean child age of 23 mo.

A total of 295 of the 371 enrolled infants were included in the analyses (Supplemental Figure 1). Mother-infant dyads were excluded from the analysis due to maternal death (n = 2) or infant death (n = 18, 25% HIV-exposed). Furthermore, infants who tested positive for HIV (n = 4) were twins (n = 7 pairs) and women who seroconverted during the study (n = 2) were excluded because such conditions could affect infant growth and body composition.

Maternal measurements

At baseline, sociodemographic and health data, including food insecurity in the past month, were collected by trained study staff using the 9-item Individual Food Insecurity Access Scale (range: 0–27) [23]. Other maternal sociodemographic variables of interest collected at enrollment included gestational age (estimated from the last menstrual period in weeks), maternal height (cm), age (years), marital status (married or single), and parity (number of pregnancies collected, dichotomized for analysis as 0 or $\geq$1). Data on breastfeeding initiation and duration were collected at 3 and 6 months postpartum. Maternal ART regimen information was collected at all visits and none of the women reported switching regimens during the study period.

Infant measurements

A range of sociodemographic and health data were collected throughout the study. Infants were classified as being born during the hunger season if their birthdays fell between or on 1 February and 31 May, as done in previous work [19]. The sexes of 44 infants were unknown, although 32 of those were identified from traditional Kenyan male or female names and were included in the analysis. Missing birthdates for 4 infants were estimated from the expected due date of the mothers.

Infant body composition measurements were completed by trained staff during all in-person infant study visits. The training of Pith Moromo staff on the collection of maternal and neonatal anthropometric and body composition measurements was overseen by a registered dietician experienced in anthropometry training. Staff were also trained in quality assurance and quality

control for anthropometric measurements. After the initial training session, monthly checks were completed to ensure that the measurements were within an acceptable range of measurement error. After completing the quality assurance and quality control measurements, intra- and interobserver differences were evaluated by the project coordinators (a research nurse and a registered dietician) and training was conducted again if needed. Each study staff member was provided with training materials and study coordinators regularly monitored the study procedures to ensure accurate measurement before staff member certification.

Skinfold measurements (mm) at the iliac crest, triceps, subscapular, and mid-thigh were obtained using Harpenden calipers (Baty International, United Kingdom). At each visit, infant weight (kg; Seca 874), length (cm; Seca 417), head circumference (cm; nonstretchable retractable tape measure), and middle-upper arm circumference (MUAC; cm; nonstretchable retractable tape measure) were also obtained, from which the arm fat area and arm muscle area (cm^2) were calculated [24]. The mean of $\geq$2 repeated measurements was calculated for greater accuracy. Growth measurements were assessed for biological implausibility (e.g., reduction in length) using growth curves and clinical judgment. We calculated all WHO *z*-scores using the "zanthro" command in the program Stata [25]. These WHO *z*-scores included length-for-age *z*-score (LAZ), weight-for-age *z*-score (WAZ), weight-for-length *z*-score (WLZ), and head circumference-for-age *z*-score (HCAZ). A total of 27 individual observations from 25 infants with LAZ ≤ -6.0, WAZ ≤ -5.0, or WLZ ≥ 5.0 were excluded from the analysis due to implausibility based on previously published standards by the WHO [26]. Raw MUAC values were used rather than MUAC *z*-scores because WHO MUAC-for-age *z*-scores are not available for infants <3 mo, which would have limited the ability to assess acute malnutrition [27]. Our measurement of regional body composition, the sum of skinfolds, was calculated by combining triceps, subscapular, iliac crest, and mid-thigh skinfolds to operationalize the subcutaneous trunk and limb adiposity. Absolute skinfold thickness values were used rather than predictive equations estimating fat and fat-free mass, as the use of absolute skinfold thickness values is recommended for examining subcutaneous adipose tissue changes longitudinally in infants and toddlers [28]. Moreover, valid predictive equations for fat mass and fat-free mass estimation and changes over time with repeated close measurements were not available for this population.

Ethics

The Institutional Review Boards at Cornell University, Northwestern University, and Kenya Medical Research Institute approved the study procedures. All mothers provided written informed consent.

Statistical analysis

Independent *t*-tests were conducted to assess differences between mother-infant dyads based on maternal HIV status, as well as to assess differences in baseline characteristics between those included and excluded in the analyses. Statistical analyses were conducted using a significance level (α) of <0.05. Infants needed to have measurements from $\geq$2 visits for a growth measure to be included in the respective analysis (e.g., 2 length measurements needed to be included in the length analysis).

LCMM

The LCMM package in R expands on the functionality of traditional linear mixed models to identify potentially asymmetrical underlying distributions of longitudinal variables [22]. This allows for the identification of subgroups (classes) within a sample with similar growth trends over time rather than assuming equal growth of all participants. The rationale and approach for LCMM are described in Table 2. For each growth model, 2–7 classes were examined to identify the optimal model fit and the number of classes per model. The number of latent trajectory classes was determined by minimizing the Bayesian Information Criterion and assessing class size to maintain a sufficient number of infants per class to support subsequent analyses (i.e., ensure that no class represented <10% of the sample). LCMM assigned infants to the class where they had the highest probability of membership for each anthropometric model independently. LCMM was applied to infant growth trajectories for LAZ, WAZ, WLZ, HCAZ, MUAC, sum of skinfolds, arm fat area, and arm muscle area.

After selecting the most suitable LCMM model for each infant outcome, multinomial logistic regression was used to determine the predictors of latent trajectory class membership. These models were constructed to separately examine the relationships with the primary exposures of interest, namely, maternal HIV status and food insecurity scores, as well as other covariates, including maternal height, maternal age, infant sex, exclusive breastfeeding at 3 months of age, and hunger season. Covariates were independently examined for their relationship with the dependent variable and those that improved the model fit were retained in the final regression models. Infant sex was not used as a covariate in models using sex-specific WHO *z*-scores. The trajectory class with the largest initial measurement was used as the reference group in each model to facilitate interpretation and reduce standard errors.

Sensitivity analyses

To examine whether maternal ART regimen was associated with growth, a sensitivity analysis was conducted among the HIV-exposed subset of the cohort examined using LCMM by examining whether the primary exposures (HIV and food insecurity) changed by $\geq$10% after adjustment for ART using chi-square analysis. Moreover, as we provided the input for infant sex (n = 32) and birthdate (n = 4) for 36 infants, we compared the baseline characteristics after exclusion and examined whether excluding these infants from the multinomial logistic regression analyses using previously fitted LCMM classes changed the effect size for the primary exposures (HIV and food insecurity) by $\geq$10%.

Results

A total of 295 (149 HIV-exposed and 146 HIV-unexposed) infants were included in the analyses with a mean of 6 in-person follow-up visits (range: 2–7) during the first 2 years of life. Maternal characteristics at baseline were similar between mother-infant dyads who were excluded and those who were included in the analyses (Supplemental Table 1).

Mothers of HIV-unexposed infants were younger, nulliparous, and had greater gestational age at enrollment compared to those living with HIV (Table 1). Maternal food insecurity scores did not

differ according to maternal HIV status and were relatively stable throughout the study follow-up period (pregnancy to 21 months postpartum). A greater proportion of HIV-exposed infants were born during the hunger season than the HIV-unexposed ones, although there were no major effects of the hunger season on the growth measures, and effects of HIV exposure on growth outcomes did not vary according to the hunger season when examined using statistical interactions (data not shown). Compared to HIV-unexposed infants, a greater proportion of HIV-exposed infants were exclusively breastfed at both 3 and 6 months of age.

Mean body composition and growth trajectories for the entire analytic sample, which was fitted using the "geom smooth" function of ggplot [29] and by treating the data as cross-sectional (Note: all *y*-axes are not the same and depend on the values for the growth measure), are presented in Figure 1. Using the same methodology, body composition and growth trajectories stratified by HIV exposure status are presented in Supplemental Figure 2. Overall, the growth of all infants in this cohort over the first 23 months was suboptimal, and even less so for HIV-exposed infants.

Growth modeling with LCMM identified 3 latent growth trajectory classes for the LAZ, WAZ, HCAZ, and arm muscle area (Figure 2) and 4 latent growth trajectory classes for the WLZ, MUAC, sum of skinfolds, and arm fat area (Figure 3). HIV-exposed infants were generally more likely to belong to the smaller growth and body composition trajectory classes than the HIV-unexposed infants, except for the sum of skinfolds (Figures 2 and 3; Supplemental Table 2). Furthermore, the likelihood of belonging to the smaller growth trajectory classes increased for HIV-exposed infants across each class for each anthropometric indicator, except for the sum of skinfolds. These LCMM results add nuance to Figure 1 by demonstrating that subgroups of growth exist within a sample of the population.

TABLE 2
Overview of the analytic approach to growth modeling

	Latent class mixture modeling
What the method does	Estimates patterns of change in subgroups in growth measurements over time.
When to use	When assessing growth parameters that are longitudinally collected in a population that may have heterogeneity in growth.
Strengths	Can identify subgroups within a sample that experience unique growth patterns; these subtleties are often overlooked when only examining mean values or the whole population rather than particular subgroups.
Limitations	The interpretation may be difficult as classes are not meaningful in and of themselves, but only relative to other groups. Need to have a larger sample size for the package to mathematically create growth trajectory subgroups.

TABLE 1
Characteristics of mother-infant dyads included in the analytic sample of the Pith Moromo cohort from Western Kenya

Studied parameters	All (n = 295)	HIV+ Mother (n = 149)	HIV− Mother (n = 146)	*P* value[1]
Maternal				
Age, y	24.8 ± 4.9[2]	26.2 ± 4.9	23.4 ± 4.4	<0.001
First pregnancy	63 (21.2)[3]	18 (12.3)	44 (30.1)	<0.001
Married	278 (94.2)	142 (95.3)	135 (92.5)	0.42
Gestational age at enrollment, wk	23.2 ± 4.6	22.5 ± 4.8	23.8 ± 4.3	0.01
Baseline height, cm	161.7 ± 7.05	161.9 ± 6.9	161.5 ± 7.2	0.63
Baseline food insecurity score (0–27)	12.8 ± 5.1	12.8 ± 5.1	12.8 ± 5.1	0.92
ART regimen				
Lopinavir/Ritonavir		4 (2.7%)		
Efavirenz		92 (61.7%)		
Nevirapine		52 (34.9%)		
Zidovudine		1 (0.7%)		
Infant				
Male sex	148 (50.2)	78 (52.3)	70 (47.9)	0.37
Born during the hunger season	163 (55.3)	69 (46.3)	94 (64.4)	0.0017
Exclusively breastfed at 3 mo	161 (54.4)	96 (64.4)	65 (44.2)	<0.001
Exclusively breastfed at 6 mo	67 (22.6)	50 (33.6)	17 (11.6)	<0.001
Age of food introduction, d	118.2 ± 78.3	140.8 ± 71.8	100.1 ± 78.6	<0.001
Age at the first visit, d	47.2 ± 12.5	46.9 ± 10.9	47.4 ± 13.9	0.72
Age at the last visit, mo	22.5 ± 1.5	22.5 ± 1.4	22.6 ± 1.6	0.52
LAZ at the first visit	−1.07 ± 1.83	−1.03 ± 1.85	−1.10 ± 1.83	0.79
LAZ at the last visit	−1.6 ± 1.31	−1.76 ± 1.08	−1.45 ± 1.5	0.14
WAZ at the first visit	−0.14 ± 1.13	−0.31 ± 1.10	−0.01 ± 1.13	0.06
WAZ at the last visit	−0.44 ± 1.18	−0.67 ± 1.0	−0.18 ± 1.30	0.006
HCZ at the first visit	0.37 ± 1.18	0.20 ± 1.0	0.53 ± 1.30	0.025
HCZ at the last visit	0.12 ± 1.07	−0.15 ± 0.98	0.41 ± 1.10	<0.001
WLZ at the first visit	0.89 ± 1.74	0.87 ± 1.74	0.90 ± 1.75	0.92
WLZ at the last visit	0.54 ± 1.2	0.33 ± 1.08	0.77 ± 1.3	0.02

[1] Comparisons between HIV− and HIV+ women were conducted using parametric tests for continuous, normally distributed variables and nonparametric tests for nonnormally distributed variables. ART, antiretroviral therapy; HCZ, head circumference-for-age *z*-score; LAZ, length-for-age *z*-score; WAZ, weight-for-age *z*-scores; WLZ, weight-for-length *z*-score.
[2] Mean ± SD (all such values).
[3] n (%) (all such values).

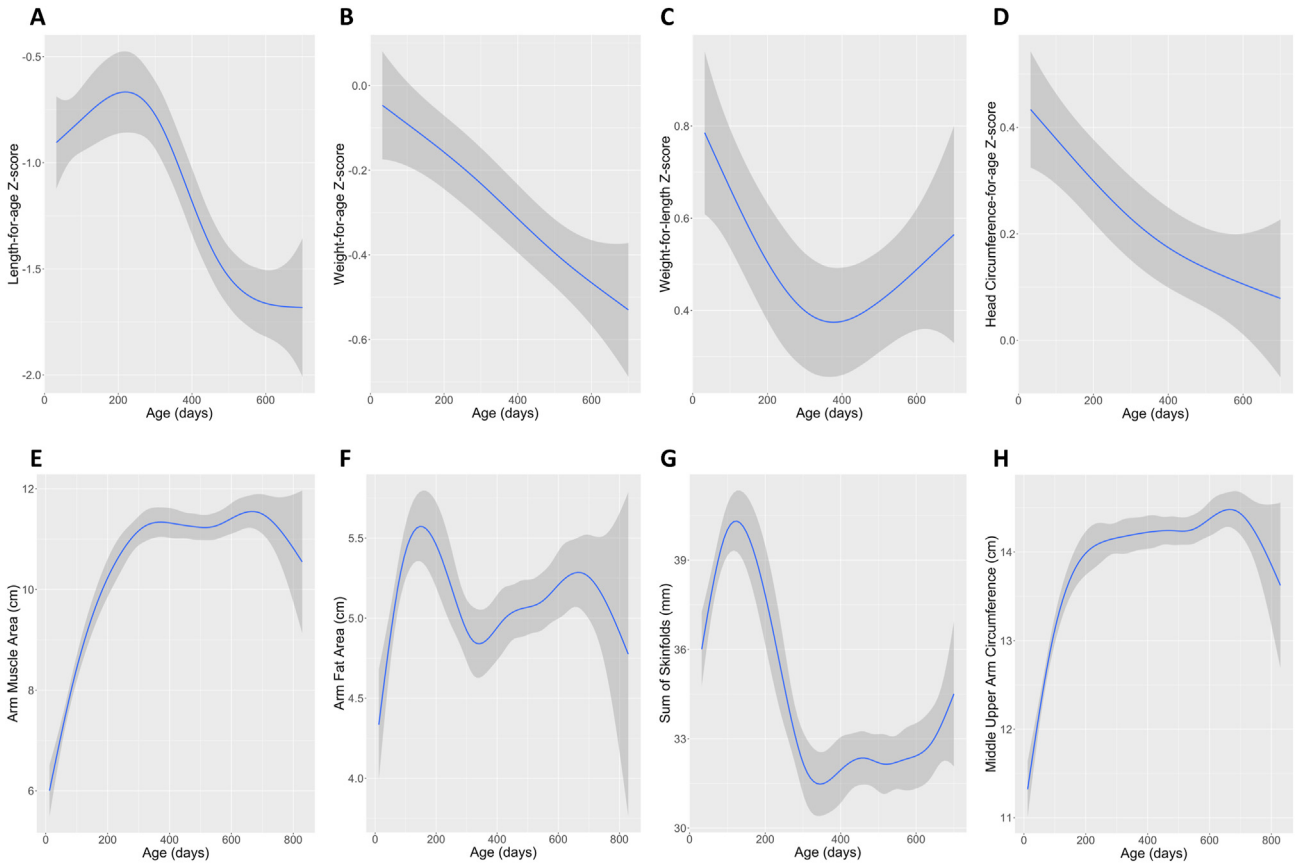

FIGURE 1. Unadjusted growth plots of all infants included in the analytic sample from 6 weeks to 23 months in Kenyan infants in the Pith Moromo study. Growth plots for all growth and body composition measurements are shown. The *y*-axes are different for each measurement as they depend on the anthropometric values or *z*-score value because of which, some axes do not start at zero.

Several additional predictors of growth and body composition trajectories were identified through the first 23 months. Infants whose mothers had higher food insecurity scores prenatally were more likely to belong to the smaller growth trajectory classes for LAZ and arm muscle area but were less likely to belong to smaller WLZ classes. For example, a 1 unit increase in prenatal food insecurity score was associated with a 10% increase in the likelihood of infants belonging to the LAZ trajectory group class 3, which persisted around a *z*-score of −3 (Model 1). Infants with taller mothers were less likely to belong to the smaller trajectory classes for LAZ and WAZ. Female infants were more likely to belong to the smallest body composition trajectory class for arm muscle area than males. Infants with older mothers were less likely to belong to WLZ class 2 (an initial *z*-score of +2) and class 3 (an initial *z*-score of −1), which then crossed each other at 1 year of age to essentially end where the other classes began. Lastly, infants who were exclusively breastfed at 3 months of age were more likely to belong to WLZ class 2, with a decline in *z*-scores over time.

Sensitivity analyses

The latent class trajectory membership in LCMM was not associated with the ART regimen for any of our anthropometric measures (Supplemental Table 3). For our sensitivity analyses assessing the 36 infants whose sex and birthdates were estimated, baseline characteristics were similar after the exclusion, and excluding these infants from the multinomial logistic regression analyses using previously fitted LCMM classes did not change the effect size for the primary exposures (HIV and food insecurity) by ≥10%.

Discussion

In our cohort of Kenyan HIV-exposed and unexposed uninfected infants, we sought to examine the growth trajectories and patterns during the first 2 years of life. The majority of infants in our cohort experienced poor growth for all anthropometric measures. Infants whose mothers were living with HIV and received Option B+ ART during pregnancy showed a growth deficit at birth and continued to exhibit sustained poor growth during the first 2 years of life compared to HIV-unexposed infants. These findings support our hypothesis that exposure to HIV and ART in utero is associated with poor growth patterns, thus extending existing evidence for this population.

We observed that HIV-exposed infants were more likely to show growth patterns with biologically relevant lower values. In particular, using LCMM to fit the growth trajectories, we observed suboptimal growth patterns for HIV-exposed infants for all anthropometric measures, except for the sum of skinfolds. Notably, we found that HIV-exposed infants were more likely to belong to the growth classes with *z*-scores that were 2–3 units lower than HIV-unexposed infants for clinically relevant anthropometric measurements including length, weight, and head circumference. Our LAZ model showed a notable decrease in the length-for-age around 1 year of age to a *z*-score that was more prominently seen in class 3, in which HIV-exposed infants

Model 1: Length-for-Age Z-Score

(n=278; average 5.1 measurements/infant)	**Class 1** (n=43, 30% HEU)	**Class 2** (n=129, 52% HEU)	**Class 3** (n=106, 56% HEU)
HIV Positive Mother	Reference	2.3 (1.1, 5.1)	3.3 (1.5, 7.4)
Food Insecurity Score (0-27)	Reference	1.05 (0.97, 1.1)	1.1 (1.01, 1.2)
Maternal Height (cm)	Reference	0.92 (0.87, 0.98)	0.89 (0.84, 0.95)
Exclusively Breastfed at 3-months of Age	Reference	1.7 (0.81, 3.6)	0.88 (0.4, 1.9)

Model 2: Weight-for-Age Z-Score

(n=278; average 5.0 measurements/infant)	**Class 1** (n=58, 33% HEU)	**Class 2** (n=158, 51% HEU)	**Class 3** (n=62, 65% HEU)
HIV Positive Mother	Reference	2.4 (1.2, 4.6)	4.2 (1.9, 9.3)
Food Insecurity Score (0-27)	Reference	1.02 (0.96, 1.1)	0.96 (0.9, 1.04)
Maternal Height (cm)	Reference	0.91 (0.86, 0.96)	0.89 (0.8, 0.9)
Exclusively Breastfed at 3-months of Age	Reference	0.93 (0.48, 1.8)	0.99 (0.4, 2.2)

Model 3: Head Circumference-for-Age Z-Score

(n=287; average 5.3 measurements/infant)	**Class 1** (n=74, 34% HEU)	**Class 2** (n=135, 50% HEU)	**Class 3** (n=78, 63% HEU)
HIV Positive Mother	Reference	2.5 (1.3, 4.7)	4.4 (2.1, 9.1)
Food Insecurity Score (0-27)	Reference	1.0 (0.95, 1.1)	0.99 (0.93, 1.1)
Maternal Age (years)	Reference	0.94 (0.88, 0.99)	0.97 (0.9, 1.04)
Exclusively Breastfed at 3-months of Age	Reference	0.75 (0.41, 1.4)	0.52 (0.3, 1.03)

Model 4: Arm Muscle Area

(n=293; average 5.5 measurements/infant)	**Class 1** (n=62, 30% HEU)	**Class 2** (n=147, 55% HEU)	**Class 3** (n=84, 57% HEU)
HIV Positive Mother	Reference	3.1 (1.6, 5.9)	3.3 (1.6, 6.8)
Food Insecurity Score (0-27)	Reference	1.1 (1.01, 1.1)	1.1 (1.01, 1.2)
Infant Sex (Female)	Reference	1.6 (0.83, 2.9)	2.5 (1.3, 5.1)

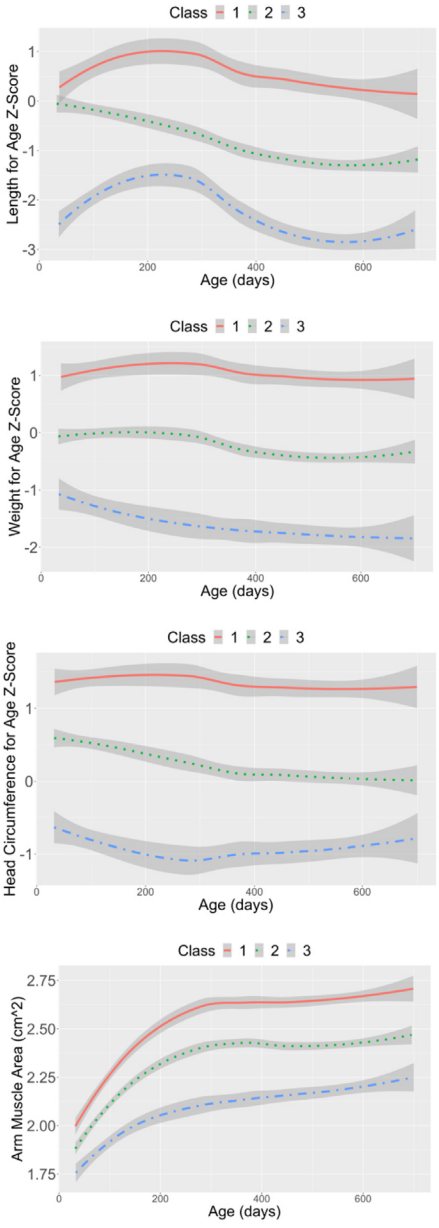

FIGURE 2. Three-class latent class mixed models and corresponding multinomial logistic regression estimates showing the relative risk ratio (95% CI) for the likelihood of being in each class relative to the reference class. Trends of trajectory classes by anthropometric measures indicate that subgroups experience distinct differences in growth patterns over time.

were >3 times more likely to belong, compared to class 1 which had the highest LAZ scores. In our WLZ model, HIV-exposed infants were 160 times more likely to belong to class 4 that started with suboptimal *z*-scores and continually experienced poorer growth in weight compared to length over time. Together, these findings suggest that HIV-exposed infants are born with poorer body composition, thus reflecting the impact of the prenatal period on fetal growth and the persistence of these adverse effects over time.

Methodologies such as LCMM, which permit flexibility in analyses for growth and body composition, are important for the overall assessment of longitudinal growth data. This method allowed us to visualize the varying growth and body composition patterns that existed in our study population. This method enhanced our understanding of the growth and body composition in any population but was particularly helpful in understanding whether high-risk groups such as HIV-exposed infants showed fundamentally different growth patterns compared to a reference standard (i.e., the WHO growth standards), which may have lasting health implications. Our findings demonstrate consistent growth differences between HIV-exposed and HIV-unexposed infants that continue to persist after the implementation of Option B+ ART and emphasize that this disparity still needs to be addressed.

Five other published studies have analyzed the growth of HIV-exposed infants subjected to ART in utero, although only 2

Model 5: Weight-for-Length Z-Score

(n=277; average 4.6 measurements/infant)	**Class 1** (n=80, 38% HEU)	**Class 2** (n=78, 50% HEU)	**Class 3** (n=60, 55% HEU)	**Class 4** (n=59, 64% HEU)
HIV Positive Mother	Reference	1.6 (0.8, 3.2)	2.2 (1.04, 4.5)	2.6 (1.2, 5.5)
Food Insecurity Score (0-27)	Reference	0.95 (0.89, 1.01)	0.98 (0.92, 1.1)	0.92 (0.86, 0.99)
Maternal Age (years)	Reference	0.93 (0.87, 0.99)	0.93 (0.8, 0.99)	1.0 (0.93, 1.1)
Exclusively Breastfed at 3-months of Age	Reference	2.3 (1.2, 4.5)	1.7 (0.8, 3.5)	1.6 (0.8, 3.4)

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Model 6: Middle Upper Arm Circumference, cm

(n=293; average 4.5 measurements/infant)	**Class 1** (n=28, 14% HEU)	**Class 2** (n=115, 51% HEU)	**Class 3** (n=127, 54% HEU)	**Class 4** (n=23, 60% HEU)
HIV Positive Mother	Reference	5.8 (1.9, 18.3)	6.8 (2.1, 21.4)	11.7 (2.9, 47.3)
Food Insecurity Score (0-27)	Reference	1.05 (0.96, 1.1)	1.1 (.97, 1.2)	1.1 (0.97, 1.2)
Maternal Height (cm)	Reference	0.97 (0.9, 1.1)	0.94 (0.9, 1.01)	0.92 (0.84, 1.01)
Exclusively Breastfed at 3-months of Age	Reference	1.3 (0.55, 3.2)	1.1 (0.45, 2.6)	0.93 (0.29, 3.0)

Model 7: Sum of Skinfolds, mm

(n=287; average 4.2 measurements/infant)	**Class 1** (n=53, 44% HEU)	**Class 2** (n=109, 48% HEU)	**Class 3** (n=78, 54% HEU)	**Class 4** (n=47, 53% HEU)
HIV Positive Mother	Reference	1.1 (0.59, 2.2)	1.4 (0.71, 2.9)	1.4 (0.63, 3.1)
Food Insecurity Score (0-27)	Reference	1.0 (0.95, 1.1)	0.99 (0.93, 1.1)	1.0 (0.93, 1.1)
Infant Sex (Female)	Reference	0.90 (0.48, 1.8)	0.70 (0.34, 1.4)	0.64 (0.29, 1.4)

Model 8: Arm Fat Area

(n=293; average 5.5 measurements/infant)	**Class 1** (n=48, 28% HEU)	**Class 2** (n=68, 49% HEU)	**Class 3** (n=93, 53% HEU)	**Class 4** (n=84, 61% HEU)
HIV Positive Mother	Reference	2.6 (1.1, 5.7)	2.9 (1.3, 6.1)	4.1 (1.9, 8.9)
Food Insecurity Score (0-27)	Reference	1.0 (0.94, 1.1)	0.97 (0.9, 1.04)	1.0 (0.93, 1.1)
Infant Sex (Female)	Reference	1.18 (0.56, 2.5)	1.02 (0.5, 2.1)	1.2 (0.6, 2.5)

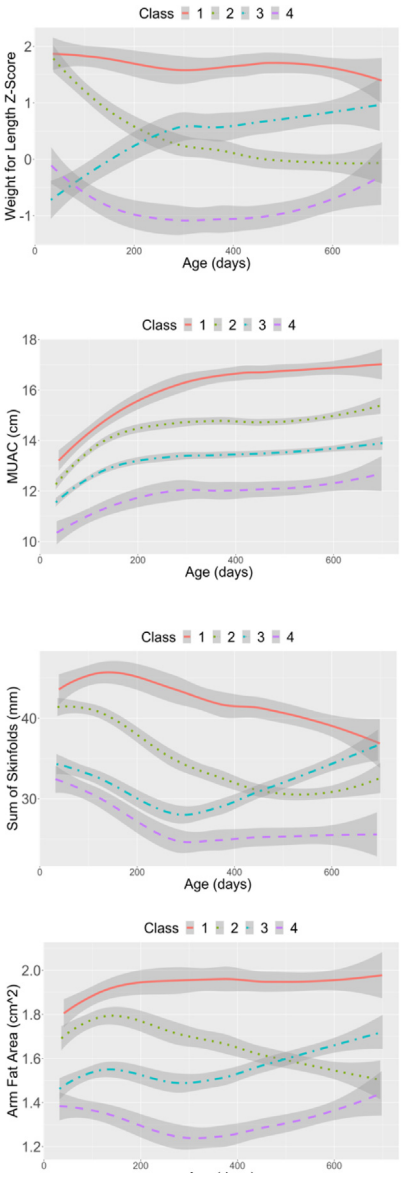

FIGURE 3. Four-class latent class mixed models and corresponding multinomial logistic regression estimates showing the relative risk ratio (95% CI) for the likelihood of being in each class relative to the reference class. Trends of trajectory classes by anthropometric measures indicate that subgroups experience distinct differences in growth patterns over time.

have done so during the second year of life [30–34]. We previously applied LCMM in a cohort of HIV-exposed and HIV-unexposed infants in Gulu, Uganda to evaluate how HIV exposure and food insecurity influenced growth and changes in body composition during the first year of life. Similar to our current findings for the length and arm fat area, HIV-exposed infants in the Ugandan cohort were more likely to belong to the shortest 2 of 4 LAZ trajectory classes [odds ratio (OR) = 3.80, 95% CI: 1.22–11.82; OR = 8.72, 95% CI: 1.80–42.09] and were more likely to show smaller arm fat area trajectories [OR = 0.86; 95% CI (0.76–0.98)] [30]. In contrast, in a cohort of Zambian infants, no differences in the linear growth velocity, estimated using mixed effect models by HIV exposure, were observed, although the entire cohort had poor linear growth, while weight and body composition were not reported and growth trajectory patterns were examined using a different method that assumes similar patterns across the population [34]. The other 3 studies used fewer measures for growth and body composition during infancy [32], did not include HIV-unexposed infants for comparison [31] or had a 1 year follow-up period [33], which makes it difficult to compare them with our study. Overall, we and others have previously found that HIV-exposed infants are more likely to have suboptimal growth overall, reduced LAZ scores, and lower arm fat area scores during infancy. To our knowledge, our paper is the first to collectively examine growth and body composition measures into the second year of life for both HIV-exposed uninfected and HIV-unexposed uninfected infants, thus advancing previous research conducted in this field.

Our second hypothesis that food insecurity would be associated with suboptimal growth patterns identified with each method was supported by only some of our findings. In our analyses using LCMM, higher prenatal food insecurity scores were

associated with smaller LAZ trajectory growth classes, as well as the 2 lower growth classes for the arm muscle area. This relationship of food insecurity with LAZ and arm muscle area suggests that prenatal food insecurity may have lasting implications for child linear growth and lean tissue changes. Several reports have shown that women living with HIV and their infants also face a greater risk of food insecurity [17, 18]. Studies from Uganda and Kenya also reported minor adverse effects of household food insecurity on some growth parameters of children 2 years of age, [30, 35], which agreed with our findings.

This paper has several strengths, including the longitudinal design, frequency of measurements, and the inclusion of HIV-exposed and HIV-unexposed infants. One limitation of this study was the varying sample size for each outcome, resulting in different numbers of infants in each model and, therefore, challenges in comparing models. We also could not discern whether the suboptimal growth patterns were attributable to HIV, ART type, length of ART exposure, or another unmeasured confounder, although we did perform a sensitivity analysis to assess if ART influenced growth in the models and found that it did not have any effect. Unfortunately, we did not have data on the length of ART exposure or whether women living with HIV received ART before the index pregnancy. Another possible limitation is that we did not include data regarding infant feeding or maternal prenatal diet. This decision was made because our objective was to assess the association of HIV exposure and food insecurity with growth and not the mediating effects of infant feeding practices. A further shortcoming is the missing data of 12 infants that were not included in any analyses because their sex was unknown or they had such suboptimal growth that their z-scores could not be calculated. These WHO *z*-score cutoff points resulted in the loss of a few observations that could have been relevant to this population, thus potentially impacting our findings with *z*-score measurements.

The findings of this study have implications for developing beneficial public health initiatives and advancing research on longitudinal body composition and growth. LCMM is a method that can be used for advancing research on growth modeling in this population, as HIV exposure is a prenatal exposure that may have lasting effects and does not vary over time like dietary exposures. Our findings highlight where interventions for growth during the first 2 years of life may be provided, as the LCMM growth plots make it easier to identify the timing of growth faltering or poor growth patterns, and could be employed in future work. As LCMM results can be subjective based on how the models were chosen, it would be imperative to apply clinical judgment when using these results in practice.

Our results from this cohort also highlight the need for prenatal interventions to support pregnant women living with HIV and ensure that they receive optimal nutrition and improve their food insecurity. These interventions would be beneficial, as our growth modeling results showed that HIV exposure was associated with poor infant growth and body composition starting at birth and continuing over the first 2 years of life. Interventions for growth could also be implemented earlier if suboptimal growth patterns like those observed in this study begin to arise. Assessing growth patterns with LCMM trajectory classes and multinomial logistic regression helped us identify the characteristics associated with growth faltering, which could also be leveraged for preventative care for HIV-exposed children.

In conclusion, our cohort of Kenyan HIV-exposed uninfected infants grew suboptimally during the first 2 years of life compared to their unexposed uninfected counterparts, with the length beginning to vacillate around 1 year of age. Innovative analytic techniques such as LCMM revealed that growth patterns shift after 1 year and that HIV-exposed infants appear to begin their infant stage at a disadvantage for growth that is sustained across infancy and into toddlerhood. This analytic technique is useful for evaluating different components of growth in relation to prenatal predictors or later health outcomes. To better support optimal growth and the overall health of HIV-exposed uninfected children, future studies should consider using advanced longitudinal growth modeling, while interventions are needed to support pregnant and postpartum mothers living with HIV, as well as their infants, to support both mother and child health.

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Disclaimer

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Data availability

Data described in the manuscript will be made available upon reasonable request to EMW and SLY. Analytic code will be available from RRR upon request pending application and approval.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2022.11.010.

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