COFACTORS OF LONGITUDINAL LINEAR GROWTH AMONG INFANTS WITH AND WITHOUT IN-UTERO HIV/ANTIRETROVIRAL EXPOSURE IN KENYA

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Abstract

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Effective treatments have decreased vertical transmission of HIV and most infants born to women living with HIV (WLH) are HIV-exposed but uninfected (HEU). There is evidence that HEU infants have poorer growth than HIV-unexposed uninfected children (HUU). The biological and social mechanisms for growth deficits in HEU are unclear. There are few large studies comparing HEU and HUU in the era of dolutegravir antiretroviral treatment (ART). WLH may be at higher risk for concurrent illnesses, mental health challenges, food insecurity, and low social support, all of which may influence infant growth and development. We leveraged data from maternal-infant dyads living in Western Kenya (n =1000 HEU, n=1000 HUU) to determine biological and social factors affecting longitudinal infant growth (length and weight-for-age z-scores [LAZ, WAZ] and weight for length z-scores[WLZ]) and stunting (LAZ<-2, underweight (WAZ<-2), and wasting (WLZ<-2)) from birth to 1 year. We found a higher prevalence of stunting, underweight, and wasting and lower length and weight for HEU compared to HUU infants. HEU infants had lower LAZ at 6 and 12 months, but not WAZ or WLZ. In the combined cohort of HEU and HUU, maternal age, lower education, intimate partner violence (IPV), maternal and infant morbidity, and food insecurity were associated with growth deficits, with some of these factors detected in stratified HEU or HUU subcohorts. High levels of social support were protective for LAZ. Among HEU, ART regimen and timing (pre- vs. post-pregnancy) did not affect growth trajectories. Addressing comorbidities, education, food insecurity, and IPV and amplifying social support may improve growth outcomes overall and among HEU.

INTRODUCTION

As effective treatments have decreased vertical transmission of HIV, most infants born to women living with HIV (WLH) are HIV-exposed but uninfected (HEU). An estimated 11.1-18.3 million children globally are HEU[1] and may have greater morbidity and mortality than HIV-unexposed uninfected children (HUU)[2–4]. Several studies have demonstrated growth deficits among HEU [2,5–7]. The mechanisms leading to poorer growth among HEU infants are not well defined. Human linear growth is influenced by genetics, multiple biological systems, and socioecological influences[8,9]. In particular, infant growth trajectories and growth faltering among HEU and HUU are modulated both by "HIV-specific factors" such as exposure to maternal viremia or immune activation, antiretroviral treatment (ART) regimens and timing, and by "universal factors" (See Wedderburn 2019 for a review and Figure 1) from suboptimal breastfeeding practices, child and maternal illness, food insecurity, disadvantaged parental mental health, and low social support[10].

Cumulative effects of universal factors on infant growth may differ for women living with HIV as compared to mothers who do not live with HIV. Women living with HIV are more likely to experience concurrent illnesses than HIV negative individuals, and may be at higher risk for mental health challenges, food insecurity, and low social support [11,12]. Concurrent upper respiratory infections (e.g., pneumonia), infectious and noninfectious diseases (e.g., tuberculosis, malaria), diarrhea, fever, and mental health challenges (including anxiety and depression) may be exacerbated in contexts of low social and material support and confer varied impacts on infant growth[13]. Depression and anxiety may influence feeding decisions, breast milk let down, or maternal-infant attachment [14–16]. Reduced or altered caregiving resultant from depression may amplify poor growth outcomes [15,17,18], though the temporal effects are unclear [19]. Additionally, food insecurity and HIV infection have synergistic impacts on maternal depression and shorter breast feeding (BF) duration in some contexts[20,21].

In addition to universal pathways, HIV-specific pathways[10] which affect WLH such as maternal viral load, immune activation, and toxicity from ART exposures may also impact infant growth among HEU infants but are less well established [103,6,22]. While HIV viral suppression has improved in the post ART era, specific ART regimens and the timing and duration of ART may impact both maternal health [23] and infant growth. In a randomized control trial (RCT) in Ethiopia, HEU infants had poorer growth outcomes when exposed to maternal ART later compared to earlier in pregnancy, whereas a U.S. study found no differences, suggesting viral load may hold more relative influence on growth than ART regimen [24,25]. ART may have indirect *positive* impacts on infant health by decreasing proinflammatory cytokines and decreasing opportunistic infections [26]. At the same time, ART exposure may alter the growth hormone axis [10,26 27]. For example, one study found HEU compared to HUU infants had lower mean Insulin-like Growth Factor 1 at six weeks and this was associated with poorer linear and ponderal growth at six months of age[27]. As both universal and HIV-specific determinants[10] may lead to further evidence of differences in growth in HEU compared to HUU infants, analyzing these factors in tandem is an important step in identifying potential mechanisms of growth faltering as well as protective effects on growth.

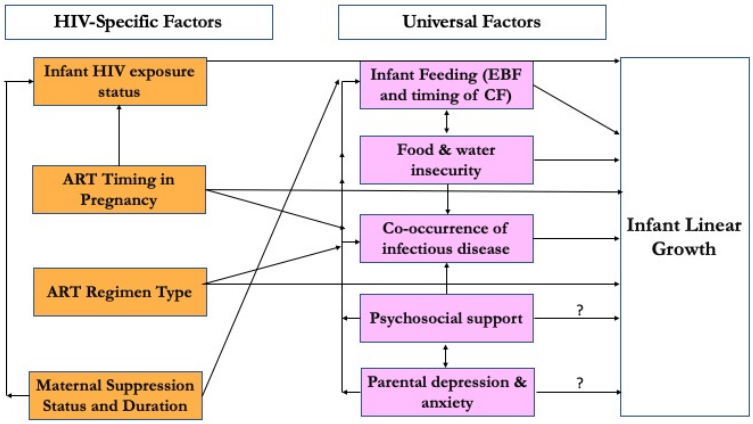

Figure 1. Conceptual Pathways of HIV specific and Universal Factors on Infant Growth

METHODS

Study design, setting, population, and data sources

Data for this analysis was obtained from the *HEU outcomes: population-evaluation and screening strategies* (HOPE) study, a longitudinal cohort study that aimed to compare 3-year clinical outcomes among HEU/HUU children in Kenya. This analysis utilized data collected through infant age of 1 year. HEU and HUU mother-infant pairs were enrolled at 6 weeks postpartum during routine postnatal care visits and followed up every 6 months until 1 year. Recruitment was done in seven public sector maternal

and child health clinics, 3 in Nairobi (Mathare, Riruta, and Kayole II) and four in Western Kenya (Kisumu County, Lumumba, Migosi, and Rachuonyo). Study inclusion criteria included mothers age >18 years old, no plans to relocate outside the study catchment area, and willing to enroll. Infant eligibility criteria included age 4-10 weeks and no gross congenital defects, history of severe birth asphyxia, or a positive HIV test. Mothers were excluded if their HIV status was unknown and were unwilling to test.

The research team obtained informed consent, contact information, sociodemographic characteristics, obstetric and medical history (including HIV/ART history for WLH). For ART-related questions, data was collected on ART regimens and timing. Mothers were screened for depression, anxiety, general wellbeing, intimate partner violence, social support, and food security. Infant birth weight and maternal HIV status were abstracted from maternal-infant health records. Infant HIV status was confirmed by PCR at 6 weeks, 6 months, and 12 months per national guidelines. At each study visit, research study staff obtained infant anthropometric measurements (length, weight, mid upper arm circumference, and head circumference) and collected information about past and current child and maternal comorbidities and nutrition.

Ethics

Ethical permissions for this study were approved by the Kenyatta National Hospital Ethics and Research Committee (P400/07/2020) and the University of Washington Institutional Review Board (STUDY00010495). All participants provided informed consent to participate in the study.

Analysis

Data Analysis and Statistical Techniques

We hypothesized HEU infants would have slower growth trajectories than HUU infants. We also hypothesized *a priori* that reported maternal and infant illnesses in the first 6 weeks after delivery (pneumonia, tuberculosis, malaria, upper respiratory infections, malnutrition, or diarrhea > 1 month) and non-birth related hospitalizations, maternal depression and anxiety, EBF < 4 months, history of food insecurity, and poor social support would attenuate growth among both HEU and HUU, with larger effects

among HEU. We hypothesized that ART initiation during pregnancy versus before pregnancy and non DTG-based ART regimens versus EFV-based regimens would attenuate infant growth trajectories.

The present analysis was pre-registered before obtaining access to the dataset. Full details of the pre-registration including in-depth statistical plans and model equations can be found on Open Science Framework (https://osf.io/dbmg9/ or DOI 10.17605/OSF.IO/DBMG9). While we originally pre-specified we would also use Super Imposition by Translation and Rotation [37] to characterize infant growth velocities, we encountered challenges with model fitting and convergence with three time points. We intend to use SITAR in a follow-up analysis with additional timepoints beyond 1 year.

We summarized descriptive statistics using medians (interquartile range [IQR]) and proportions. We estimated prevalence ratios and 95% confidence intervals comparing HEU/HUU characteristics at baseline and growth (stunting, overweight, and wasting) (We fitted line plots of infant LAZ, WAZ, and WLZ using R package ggplot). We used linear mixed effects models (R package lme) to compare LAZ, WAZ and WLZ among HEU/HUU and determine correlates of infant growth (LAZ, WAZ, WLZ) overall and among HEU/HUU. To test our first hypothesis that growth is attenuated for HEU as compared to HUU infants, we used an interaction term between visit and HEU status on longitudinal infant growth. For analyses of the cofactors of infant growth, we tested for the independent effect of each cofactor on longitudinal Z-score outcomes accounting for within-person change over time. All analyses included an overall model (all infants) and stratified models (HEU, HUU). For models including all infants we adjusted for infant HEU status and stratified models included HEU or HUU infants only. All models were adjusted for pre-specified factors including infant birth weight, maternal age, and infant sex. All analysis was conducted using program R [version 4.3.0]. Statistical models were assessed using AIC, BIC, effect estimate size, and p-values (< alpha .05).

Measures and Variable Definitions

Primary outcomes of interest included infant weight-for-age (WAZ) , length-for-age (LAZ), and weight-for-length (WLZ) Z-scores, which were estimated according to WHO Growth Standards [28] at six weeks (enrollment, age range 4-10 weeks), 6 months, and 12 months. We also compared the proportions of HEU/HUU infants with growth Z-scores of less than –2 SD; defined as moderate to severe malnutrition

– stunting: LAZ<-2, underweight: WAZ<-2, wasting: WLZ<-2. The primary exposure of interest was infant HIV exposure (HEU/HUU).

We examined several potential cofactors that we hypothesized would influence infant growth. Cofactors included were measured at 6 weeks, including birth weight (kg), infant sex (male or female assigned at birth), maternal age (years), maternal level of education (none, primary, secondary, college, or university), whether mothers or infants were ever hospitalized for non-birth related reasons (e.g., illnesses such as pneumonia), and any illnesses mothers had self-reported at enrollment (e.g., anemia, TB, malaria, malnutrition). Exclusive breast feeding (EBF) was defined as feeding infant with breast milk alone. Other exposures of interest included patient health questionnaire-9 (PHQ-9; scores ³ categorized as scores of ≥10 [moderate or severe depression] versus <10 [mild or very little depression]) [29,30], Kessler psychological distress scale (K10; scores ³ ≥20 [mild or greater anxiety] versus <20 [little or very little anxiety]) [31,32], Multidimensional Perceived Social Support scale (MSPSS) scores categorized as low ≤ 24, medium 25-50, and high levels of social support 50-74) [33,34]. Intimate partner violence (IPV) was assessed using the Hurt, Threaten, Insult and Scream tool (HITs; scores ³ ≥10.5 [mild to severe IPV] versus <10.5 [none to mild IPV]) [35]. Food insecurity questions were assessed using the Household Food Insecurity scale (HHS) [36], which asked how often caregivers and individuals in the household had little or no food, went to sleep hungry, or went a whole day without food in the past month. Food insecurity was categorized as little (never or rarely), moderate (3-10 times), and severe (10+ times) [21,36]. ART timing was categorized as initiated ART before or after pregnancy, and ART regimens were defined as dolutegravir (DTG)-based, efavirenz (EFV)-based, or protease inhibitor (PI)-based.

RESULTS

Baseline characteristics

Of 2000 mother infant pairs enrolled, 1000 were HEU and 1000 were HUU. Baseline infant characteristics are summarized in Table 1, where specific sample sizes can be found. We maximized available data for HEU and HUU infants for each variable listed in Table 1 which explains varied sample sizes. At enrollment, compared to women not living with HIV, WLH were older (31 vs 26 years) and had a higher prevalence of being in a polygamous marriage (11.5% vs 4.2%) or being single/never married

(12.4% vs. 7.5%) or separated/widowed (1.4% vs 0.4%), having mild to severe anxiety (10% vs 7.4%), low social support (5.2% vs 3.0%), moderate food insecurity (22% vs 9%), and had a lower prevalence of secondary or higher education (38% vs 52%, 11% vs 21%) (Table 1). Infants of WLH had a lower birth weight (3200g vs 3260g), and a higher prevalence of being exclusively breastfed at 6 weeks, compared to infants of women without HIV (98.2% vs 95.6%). Among WLH, 84% initiated ART prior to pregnancy, and a majority (73%) of women were on DTG-based ART regimens. (Table 1). Overall, 5% of the infants in the study (n=106) were low birthweight babies (<2500g) but there was nonsignificant difference in LBW comparing HEU to HUU (58% of all LBW vs 42%, p=0.08). At 6 weeks, >90% of all infants were exclusively breast fed, at 6 months 51% were still exclusively breast feeding, and at 12 months 1.7%.

Overall Differences in LAZ, WAZ, and WLZ

Mean LAZ, WAZ, and WLZ scores decreased from enrollment to 12 months in all infants (Table 2, Figures 2a, 2b, 2c). HEU infants had significantly lower WAZ at 6 weeks, 6 months, and 12 months than HUU infants ($p<0.05$ for all, Table 2). There were no differences in LAZ at enrollment between HEU and HUU infants, but HEU had significantly lower LAZ than HUU infants at 6 and 12 months ($p < 0.05$). At 6 weeks HEU had a lower WLZ compared to HUU but not at 6 or 12 months.

The prevalence of stunting, wasting and underweight increased from 6 weeks to 12 months in all infants; there were significantly higher proportions of stunted and underweight HEU infants at 6 months and 12 months ($p<0.05$ (Table 2)).

In multivariate analysis examining the impact of HEU status at 6 and 12 months and adjusting for birth weight, maternal age, and infant sex, HEU infants had significantly lower LAZ at 6 months (-0.20 [-0.32, -0.08], p-value = 0.0011) and 12 months (-0.19 [-0.29, -0.09], p-value = 0.0001) (Figure 3). There were no differences in WAZ or WLZ scores at 6 or 12 months (Figure 3).

Cofactors of Longitudinal Infant LAZ, WAZ, and WLZ

We used multivariate analyses of growth in the overall cohort (adjusted for HEU status) and stratified analyses among HEU and HUU (Table 3). All of these models were adjusted for infant birth weight, infant sex, and maternal age. Higher maternal age was associated with lower WAZ scores overall

(-0.010 [-0.017, -0.003], p=0.004) and among HUU (-0.01 [-0.02, -0.001], p=0.029) and with lower overall WLZ scores overall (-0.02 [-0.02, -0.008], p=0.000) and among HEU (-0.01[-0.02, -0.0009], p=0.033) and HUU (-0.02[-0.03, -0.01], p=0.002). A higher level of education was positively associated with LAZ (0.07 [0.01, 0.12], p=0.021) in all infants, though only associated with LAZ for HUU infants in stratified models (0.08 [0.006, 0.16], p=0.033). There was a small negative association between mothers reporting any illnesses at enrollment (diarrhea > 1 month, pulmonary or extra pulmonary TB, pneumonia, anemia, malnutrition, or malaria) and LAZ (-0.09 [-0.18, -0.01], p=0.051), with larger negative effects for HUU infants in stratified models (-0.14[-0.26, -0.01], p=0.029). Infant hospitalization was negatively associated with infant WLZ overall, (-0.42 [-0.85, 0.02], p=0.056) with stronger effects for HEU infants in stratified models (-0.79[-1.43, -0.16], p=0.013). In addition, moderate food insecurity was negatively associated with WLZ for HUU infants only (-0.23 [-0.45, -0.02],p=0.033).

Greater social support reported by mothers was protective towards LAZ (0.21 [0.007,0.41], p= 0.042) and WAZ (0.20 [-0.01, 0.39], p=0.056) but not WLZ in all infants and specifically protective for HEU infants for WLZ in stratified models (0.28 [-0.007, 0.58], p=0.056) (Table 3). Lower levels of reported intimate partner violence were associated with greater LAZ in all infants, but the effect size and statistical significance of this diminished after adjustment. We did not find evidence in this sample that relationship status, maternal hospitalization in pregnancy for non-birth related events, maternal anxiety or depression, maternal wellbeing, intimate partner violence, timing of maternal ART or regimen type, or EBF at 6 weeks influenced longitudinal infant z-score outcomes.

DISCUSSION

In this large study of longitudinal growth among HEU and HUU infants in Kenya, we found a higher prevalence of stunting, underweight, and wasting and significantly lower length and weight for HEU compared to HUU infants. HEU infants had lower LAZ at 6 and 12 months, but not WAZ or WLZ. Our cohort comprised mother-infant pairs on optimized ART regimens with over 80% of mothers initiating ART pre-pregnancy and almost three quarters exposed to dolutegravir based ART regimens. Our findings are similar to a recent study comparing growth Z-scores at 6 weeks and 6 months in South Africa and Zambia, finding lower LAZ but not WAZ or WLZ at 6 months [38]. While there were not differences in LAZ at baseline, there was sustained attenuation of LAZ which may reflect pre-birth nutritional inadequacies,

fetal programming to HIV exposure that is still unknown, or specific, unmeasured biological impacts of HIV exposure on length specifically. Future research should further clarify these potential mechanisms. We made *a priori* predictions about the cofactors that may be contributing to growth outcomes based on a biocultural and ecosocial approach to infant health [39–41]. When examining cofactors of longitudinal infant LAZ, WAZ, and WLZ, we found evidence of several attenuating and protective relationships which provide useful insights about universal, HIV-specific, and socioecological factors influencing infant growth.

This HEU cohort included a large number of mothers on DTG-based ART, the currently recommended first line treatment [42]. Despite DTG-ART, growth deficits persisted. It remains unclear what the mechanism is for growth compromise among HEU infants – biological and social factors likely both play a role [9,40,43–45]. We did not find significant associations between ART regimen type or duration with growth deficits among HEU in this cohort. Our study enrolled women at a time national guidelines were changing from EFV to DTG based regimens, and some women were exposed to both regimens which enabled comparison of these two regimens. Social factors such as perceived social support and food insecurity were associated with growth overall and likely contribute to infant growth differences between HEU and HUU. In analyses adjusted for these social factors, growth deficits persisted suggesting some impact of biological factors such as in utero exposure to HIV itself, immune-growth trade-offs within infants, or maternal immune-reproductive trade-offs during pregnancy [45,46].

A social immunological approach (broadly construed) posits that society and culture influence biological and behavioral responses to infection with varied impacts on the individual and structural levels [13]. We found that maternal illness was negatively associated with LAZ for all infants. Maternal illness may have adversely affected growth indirectly through breastfeeding practices or perceived breastmilk quality[47–49]. We were surprised to find a larger effect size for the association between maternal illness and infant growth among HUU than HEU infants. This may be because in the context of maternal HIV infection, additional illness has less impact on infant growth than in the context of no maternal HIV infection. As expected, infant hospitalization due to acute illness was negatively associated with WLZ in all infants. In stratified models a robust effect (nearly double the effect size of the un-stratified model) was only found among HEU infants which may have driven the overall association, consistent with prior studies which show acute illness has short-term impacts on undernutrition among HEU [50].

Infants born to mothers with HIV may be at increased risk for low birthweight or preterm birth, which in turn can lead to long-term growth compromise. However, in our analysis, prevalence of low birth weight was relatively low and we found that higher birthweight was protective for long-term growth in all infants. We also found a positive association between male infant sex and growth z-scores, over and above use of sex-adjusted z-score estimates. Male sex has been associated with increased growth trajectories in prior literature, though the biological mechanisms underlying this remain unclear [51,52] . Mothers of HEU infants in our sample were older than mothers of HUU infants and we found small, negative associations between maternal age and WAZ and WLZ in all infants, with similar negative effects for HEU and HUU infants (Table 3).

As expected, we found an inverse association between moderate food insecurity (experienced in the prior month) and overall WLZ trajectories for HEU infants. This finding is consistent with prior research showing that women living with HIV are more likely to be food insecure and that food insecurity may attenuate growth [53,54]. Food supplementation programs in the context of maternal-child health care, particularly for women with HIV, may be useful to foster infant/child growth and development.

Lastly, we predicted that greater maternal social support, longer EBF, and fewer mental health challenges would be protective towards infant growth. High levels of reported social support were associated with greater LAZ and WAZ, and buffered WLZ among HEU. Social support levels were similar among mothers of HEU and HUU. Social support may confer nutritional benefits for infants and mothers who are facing food insecurity or generally improve infant outcomes [55,56]. Extended networks of support may allow for alloparental investment and diverse forms of care for infants, which has been shown to influence infant and child growth [57]. In HIV programs, peer-to-peer counseling is incorporated for WLH particularly during pregnancy and lactation [58,59], and these programs could be leveraged to provide more support to bolster infant growth. We found that higher maternal education level was positively associated with LAZ in all infants and among HEU. Several studies have shown that lower education level is associated with greater risks of stunting, although there are some inconsistencies between studies [60]. Programs to enhance social support postpartum for parents and infants and to provide targeted counseling on infant feeding and nutrition, may be useful, particularly tailored for educational differences among mothers.

Limitations

While our study had many strengths, including a large cohort size and longitudinal follow-up with high retention, there were some limitations. We knew for example, primigravida is a known universal factor influencing infant growth, however we did not have a survey measure capturing this. We did not have maternal CD4 data which could be relevant as an immune predictor of growth, and similarly did not have viral load data. We assessed growth at only 4 timepoints over the first year rather than monthly, limiting detailed characterization of trajectories over this period. Growth was measured by trained study nurses but could be susceptible to measurement error.

CONCLUSION

In our study of infants who were exposed and unexposed to HIV in-utero, we found that exposure to HIV in utero was associated with more stunting, wasting, or underweight in the first year of life and with lower length growth in this period. Universal and HIV-specific pathways which are mechanistically linked to infant growth via both biological and social experiences, influenced infant growth in this study. Several of the predictors we identified such as food insecurity, social support and maternal health could be addressed in maternal child health and HIV programs in order to improve infant early growth.

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TABLES AND FIGURES

Table 1. Maternal and Infant Characteristics [Median (IQR) or n (%)]

CHARACTERISTICS	n	OVERALL	n	HEU	n	HUU	PR (95% CI) or p-value*
Maternal Factors							
Age (years) (IQR)	1951	29 (9)	961	31 (8)	990	26 (7)	<0.001
Relationship Status	1973		984		989		
Married (Monogamous) [ref]		1515 (76.8%)		708 (71.9%)		807 (81.6%)	-
Married (Polygamous)		155 (7.8%)		113 (11.5%)		42 (4.2%)	2.78 (1.98, 3.91)
Steady Partner		89 (4.5%)		27 (2.7%)		62 (6.3%)	0.51 (0.33, 0.80)
Separated/Widowed		18 (0.9%)		14 (1.4%)		4 (0.4%)	3.93 (1.30, 11.89)
Never Married/Other		196 (9.9%)		122 (12.4%)		74 (7.5%)	1.75 (1.33, 2.30)
Education	1975		984		991		
None/Primary [ref]		768 (39%)		499 (51%)		269 (27%)	--
Secondary		890 (45%)		379 (38%)		511 (52%)	0.66 (0.60, 0.72)
College/University		317 (16%)		106 (11%)		211(21%)	0.40 (0.33, 0.49)
Hospitalized in pregnancy	1991	83 (4.2%)	995	47 (4.7%)	996	36 (3.6%)	1.31 (0.85, 2.00)
Reported any illnesses at 6 weeks	1989	486 (24.4 %)	995	249 (25%)	994	237 (24%)	1.05 (0.90, 1.23)
Moderate to severe depression symptoms at 6 weeks (³ moderate)	1958	48 (2.5%)	965	19 (1.9%)	993	29 (2.9%)	0.67 (0.38, 1.19)
Mild to severe anxiety symptoms	1958	171 (8.7%)	965	97 (10%)	993	74 (7.4%)	1.35 (1.01, 1.80)
Maternal Wellbeing Index score	1975	80 (28)	984	80 (32)	991	80 (28)	<0.000
Social Support	1979		987		992		
Low [ref]		81 (4.1%)		51(5.2%)		30 (3.0%)	ref
Medium		586 (29.6%)		340 (34.4%)		246 (24.7%)	0.98 (0.92, 1.03)
High		1312 (66.3%)		596 (60.3%)		716 (72.17%)	0.96 (0.93, 0.99)
Food Insecurity	1990		995		995		
Little		1672 (84%)		767 (77%)		905 (91%)	ref
Moderate		308 (15.5%)		219 (22%)		89 (9%)	2.48 (1.97, 3.12)
Severe		10 (0.5%)		9 (1%)		1 (.1%)	10.51 (1.33, 82.75)
Intimate partner violence (IPV) past 6 months (³ mild)	1959	51 (2.6%)	971	23 (2.4%)	988	28 (2.8%)	0.84 (0.48, 1.44)

Enrolled in ART pre-pregnancy	-	-	955	803 (84%)	-	-	-
ART Regimen at 6 weeks EFV-based DTG-based PI Based or Other	-	-	855	 178 (21%) 626 (73%) 51 (6%)	-	-	-
Infant Factors							
Birth weight (grams) (IQR)	1936	3200 (600)	963	3200 (600)	973	3260 (600)	0.002
Sex assigned at birth Female Male	1996	 1009 (50.5%) 987 (49.4%)	999	 497 (49.7%) 502 (50.3%)	997	 512 (51%) 485 (49 %)	 Ref 0.97 (0.89, 1.06)
EBF at 6 weeks	1986	1924 (96.8%)	990	972 (98.2%)	996	952 (95.6%)	1.03 (1.01, 1.04)
Hospitalized in first 6 weeks	1975	18 (0.9%)	984	7 (0.7%)	991	11 (1.1%)	0.64 (0.25, 1.65)

*To test for differences in the above cofactors between HEU/HUU infants, prevalence ratios and 95% CI's presented for proportions and p-values from Wilcox Rank Sum tests are presented for cofactors where medians are presented.

Table 2. Mean Differences in Infant Z-Scores and Stunting, Underweight, and Wasting among HEU and HUU

Infant Growth Outcomes	n	Overall	n	HEU	n	HUU	Statistical Difference Between HEU/HUU*
Growth Z Scores- Mean (SD)							
LAZ							
6 weeks	1975	-0.51 (1.22)	984	-0.51 (1.26)	991	-0.50 (1.19)	0.795
6 months	1792	-0.52 (1.32)	903	-0.61 (1.35)	888	-0.42 (1.27)	0.003
12 months	1705	-0.74 (1.19)	856	-0.85 (1.27)	848	-0.64 (1.10)	0.000
WAZ							
6 weeks	1975	-0.07 (1.15)	984	-0.14 (1.15)	991	0.01 (1.16)	0.006
6 months	1792	-0.16 (1.33)	903	-0.29 (1.37)	888	-0.13 (1.29)	0.030
12 months	1705	-0.33 (1.22)	856	-0.43 (1.28)	848	-0.26 (1.15)	0.040
WLZ							
6 weeks	1975	0.61 (1.26)	984	0.52 (1.28)	991	0.62 (1.24)	0.001
6 months	1792	0.22 (1.27)	903	0.18 (1.28)	888	0.25 (1.25)	0.371
12 months	1705	0.00 (1.22)	856	-0.04 (1.25)	848	0.05 (1.20)	0.350
Stunting, Underweight, and Wasting -n (%), < -2 SD							
Stunting							
6 weeks	1965	223 (12.8 %)	978	118 (12%)	987	105 (10.6%)	1.13 (0.89, 1.45)
6 months	1753	240 (13.7 %)	879	142 (16%)	874	98 (11.2%)	1.44 (1.13, 1.83)
12 months	1599	233 (14.6 %)	798	149 (18.7%)	801	84 (10.5%)	1.78 (1.39, 2.28)
Underweight							
6 weeks	1954	101 (5.2%)	972	50 (5.1%)	982	51(5.2%)	0.99 (0.68, 1.45)
6 months	1726	160 (9.3%)	873	103 (11.8%)	796	57 (7.2%)	1.77 (1.30, 2.41)
12 months	1591	127 (8.0%)	795	84 (10.6%)	796	43 (5.4%)	1.96 (1.37, 2.79)
Wasting							
6 weeks	1950	54 (2.8%)	968	29 (3.0%)	982	25 (2.5%)	1.18 (0.69, 1.99)
6 months	1733	72 (4.2%)	875	41 (4.7%)	858	31 (3.6%)	1.30 (0.82, 2.05)
12 months	1590	82 (5.2%)	794	48 (6.0%)	796	34 (4.3%)	1.42 (0.92, 2.17)

Table 3. Adjusted Impact of Cofactors at 6 weeks on longitudinal LAZ, WAZ, and WLZ*

	LAZ Adjusted Coefficient [95% CI], P-value			WAZ Adjusted Coefficient [95% CI], P-value			WLZ Adjusted Coefficient [95% CI], P-value		
	Overall	**HEU**	**HUU**	**Overall**	**HEU**	**HUU**	**Overall**	**HEU**	**HUU**
HEU Status (ref: HUU)	**-0.11[-0.19,-0.025], 0.010**	--	--	**-0.08[-0.16,0.002], 0.056**	**--**	**--**	**-0.03[-0.13, 0.06], 0.479**	**--**	**--**
Maternal Age	0.000 [-0.006, 0.007], 0.947	0.004 [-0.006, 0.014], 0.448	0.001[-0.01, 0.01], 0.789	**-0.010 [-0.017, -0.003], 0.004**	-0.005[-0.15, 0.004], 0.299	**-0.01 [-0.02, -0.001], 0.029**	**-0.02 [-0.02, -0.008], 0.000**	**-0.01[-0.02, -0.0009],0.033**	**-0.02[-0.03, -0.01], 0.002**
Education	**0.07 [0.01, 0.12], 0.021**	0.03[-0.05, 0.12], 0.437	**0.08 [0.006, 0.16], 0.033**	0.05 [-0.01, .10], 0.097	0.005[-0.08, 0.09], 0.897	0.08 [-0.004, 0.15], 0.063	0.01 [-0.05, 0.07], 0.732	-0.03[-0.12,0.06], 0.516	0.04[-0.04, 0.14], 0.324
Relationship Status	--								
Currently Partnered [ref]	-0.002 [-0.15, -0.10], 0.719	--	--	--	--	--	--	--	--
Not Currently Partnered		-0.03 [-0.20, 0.13], 0.701	0.05 [-0.14, 0.25], 0.599	-0.03[-0.16, 0.09], 0.628	-0.05 [-0.22, 0.11], 0.516	0.05[-0.14, 0.26], 0.576	-0.07[-0.21, 0.07], 0.333	-0.12[-0.30, 0.07], 0.219	0.02[-0.21, 0.25], 0.888
Hospitalized In Pregnancy	-0.15 [-0.34, 0.05], 0.139	-0.22 [-0.49, 0.04], 0.09	-0.03[-0.25, 0.31], 0.839	-0.07 [-0.26, 0.12], 0.447	-0.19[-0.44, 0.06], 0.146	0.12[-0.17,0.41], 0.414	0.13 [-0.07, 0.35], 0.210	0.02[-0.26, 0.30], 0.873	0.29[-0.03,0.62], 0.073
Depression	-0.15 [-0.41, 0.12], 0.279	-0.16 [-0.58, 0.25], 0.440	-0.14[-0.46, 0.19], 0.410	-0.03 [-0.29, 0.23], 0.809	0.02[-0.38, 0.42], 0.912	-0.06[-0.39,0.28], 0.743	0.11 [-0.18,0.39], 0.468	0.11[-0.33,0.56], 0.619	0.09[-0.28, 0.47], 0.620
Anxiety	-0.09 [-0.23,0.05], 0.193	-0.03[-0.22,0.16], 0.783	-0.18[-0.38, 0.02], 0.077	-0.07 [-0.21, 0.07], 0.323	-0.08[-0.26, 0.11], 0.404	-0.05[-0.26, 0.16], 0.645	-0.01 [-0.16, 0.15], 0.926	-0.07[-0.27, 0.14], 0.538	0.07[-0.16, 0.30], 0.558
Any illnesses reported at weeks (maternal)	**-0.09 [-0.18, -**	-0.03[-0.16,	**-0.14[-0.26, -**	-0.08 [-0.17,	-0.08[-0.20,	-0.07 [-0.21, 0.05], 0.239	-0.02 [-0.12,	-0.08[-0.22, 0.06], 0.265	0.04[-0.09,0.19], 0.537

	0.01], 0.051	0.10],0.685	**0.01], 0.029**	0.01], 0.065	0.05], 0.235		0.07], 0.673		
Maternal wellbeing	0.00 [-0.009, 0.002], 0.424	-0.001[-0.003,0.002], 0.359	0.002 [-0.0003, 0.003], 0.095	-0.001 [-0.001, 0.001], 0.871	-0.0005[-0.002, 0.002], 0.623	0.00[-0.002, 0.002], 0.981	-0.008 [-0.003, 0.007], 0.299	0.00[-0.002, 0.002], 0.896	-0.0001[-0.004, 0.0005], 0.124
Social Support									
Low [ref]	--	--	--	--	--	--	--	--	--
Medium	0.08[-0.12,0.29], 0.423	0.040[-0.23, 0.31], 0.768	0.11[-0.21, 0.43], 0.518	0.13 [-0.07, 0.33], 0.227	0.16[-0.10, 0.42], 0.237	0.03[-0.30,0.37], 0.841	0.21 [-0.02, 0.44], 0.072	**0.28 [-0.007, 0.58], 0.056**	0.07 [-0.29, 0.44], 0.695
High	**0.21 [0.007,0.41], 0.042**	0.17[-0.09, 0.43], 0.222	0.21[-0.09, 0.52], 0.180	**0.20 [-0.01, 0.39], 0.056**	0.21[-0.04,0.46], 0.097	0.10 [-0.22, 0.43], 0.528	0.20 [-0.02, 0.43], 0.074	0.26[-0.02, 0.55], 0.070	-0.08[-0.27, 0.44], 0.650
Intimate Partner Violence									
High IPV [ref]	--	--	--	--	--	--	--	--	--
Low IPV	0.20[-0.06, 0.46], 0.135	0.23[-0.18, 0.64], 0.271	0.21[-0.12, 0.55], 0.208	0.10 [-0.15, 0.36], 0.442	0.30[-0.08, 0.68], 0.130	-0.02[-0.37,0.32], 0.907	-0.10 [-0.38, 0.18], 0.498	0.11[-0.32, 0.55], 0.599	-0.26[-0.64,0.12], 0.184
Food Insecurity									
Little [ref]	--	--	--	--	--	--	--	--	--
Moderate	-0.02[-0.08, 0.13], 0.658	0.06[-0.08, 0.19], 0.440	-0.003[-0.19,0.19], 0.988	-0.02 [-0.13, 0.08], 0.677	0.02[-0.12, 0.15], 0.804	-0.07[-0.27, 0.12], 0.449	-0.11 [-0.22,0.01], 0.084	-0.05[-0.19,0.11], 0.557	**-0.23 [-0.45, -0.02],0.033**
Severe	-0.08[-0.64, 0.47], 0.771	0.13[-0.48, 0.74], 0.669	-1.1[-2.7, 0.48], 0.172	-0.11 [-0.67,0.45], 0.697	0.12[-0.48,0.71], 0.700	-1.24[-2.97, 0.43], 0.147	-0.17 [-0.78, 0.44], 0.587	-0.05[-0.71, 0.60], 0.867	-0.87[-2.7, 0.96], 0.351
ART before pregnancy	-	-0.10 [-0.27,	--	--	-0.04 [-0.20,	--	--	0.016 [-0.16, 0.19], 0.859	--

		0.06], 0.225			0.11], 0.601				
ART regimen									
DTG-based [ref]	--	--	--	--	--	--	--	--	--
EFV-based	--	-0.10 [-0.25,0.05], 0.193	--	--	0.07 [-0.21, 0.07], 0.362	--	--	-0.004 [-0.16, 0.16], 0.960	--
PI or other	--	-0.14 [-0.40, 0.11], 0.271	--	--	0.04 [-0.20, 0.29], 0.725	--	--	0.12 [-0.15, 0.39], 0.398	--
Birth weight in kg	**0.74 [0.67, 0.80], 0.000**	**0.73[0.63, 0.82], 0.000**	**0.73[0.64, 0.83], 0.000**	**0.82 [0.75,0.88], 0.000**	**0.80[0.70, 0.89], 0.000**	**0.84[0.74, 0.94], 0.000**	**0.33 [0.26, 0.41], 0.000**	**0.30[0.20, 0.41], 0.000**	**0.37[0.26,0.48], 0.000**
Infant sex assigned at birth [ref: female]	**0.85 [0.77, 0.93], 0.000**	**1.05[0.94, 1.17], 0.000**	**0.69 [0.58, 0.79], 0.000**	**0.75 [0.67,0.83], 0.000**	**0.89[0.77, 1.00], 0.000**	**0.62[0.51, 0.72], 0.000**	**0.23 [0.14,0.32], 0.000**	**0.31[0.18, 0.44], 0.000**	**0.16[0.04, 0.28], 0.011**
No Exclusive Breastfeeding [ref: EBF]	-0.04 [-0.26, 0.18], 0.704	-0.07 [-0.49, 0.34], 0.727	-0.58[-0.32, 0.20], 0.657	-0.006 [-0.23, 0.21], 0.952	-0.15[-0.55, 0.24], 0.450	0.03[-0.24, 0.30], 0.823	-0.02 [-0.27, 0.23], 0.859	-0.11[-0.55, 0.34], 0.674	0.004[-0.29, 0.30], 0.977
Infant Hospitalized	0.15 [-0.23, 0.54], 0.442	0.48[-0.09, 1.07], 0.103	-0.18[-0.68, 0.32], 0.476	-0.29 [-0.68, 0.09], 0.135	-0.46 [-1.02,0.10], 0.111	-0.22[-0.75, 0.31], 0.417	**-0.42 [-0.85, 0.02], 0.056**	**-0.79[-1.43, -0.16], 0.013**	-0.10 [-0.70, 0.49], 0.741

*All models included a random intercept and slope for visit (time) and adjustment variables: infant sex, maternal age, and infant birthweight which were pre-specified adjustment variables. Correction for autocorrelation was specified in models.

Figure 2a. Smoothed, fitted line plot of LAZ

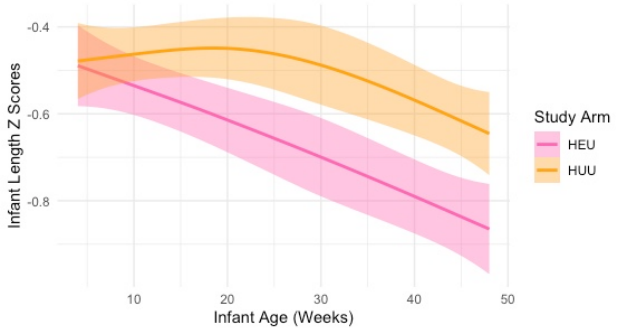


Figure 2b. Smoothed fitted line plot of WAZ

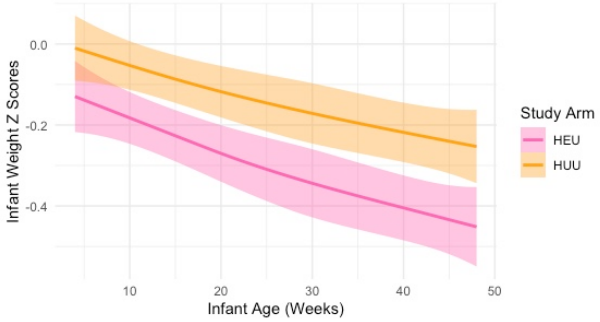


Figure 2c. Smoothed fitted line plot of WLZ

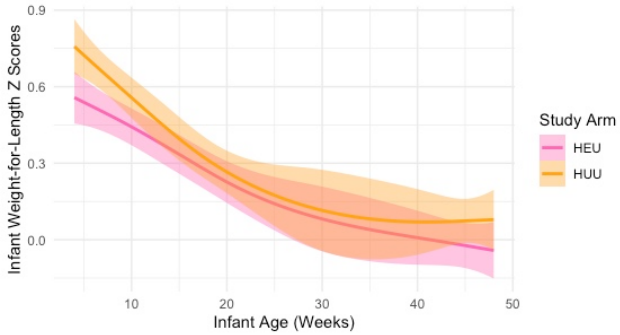
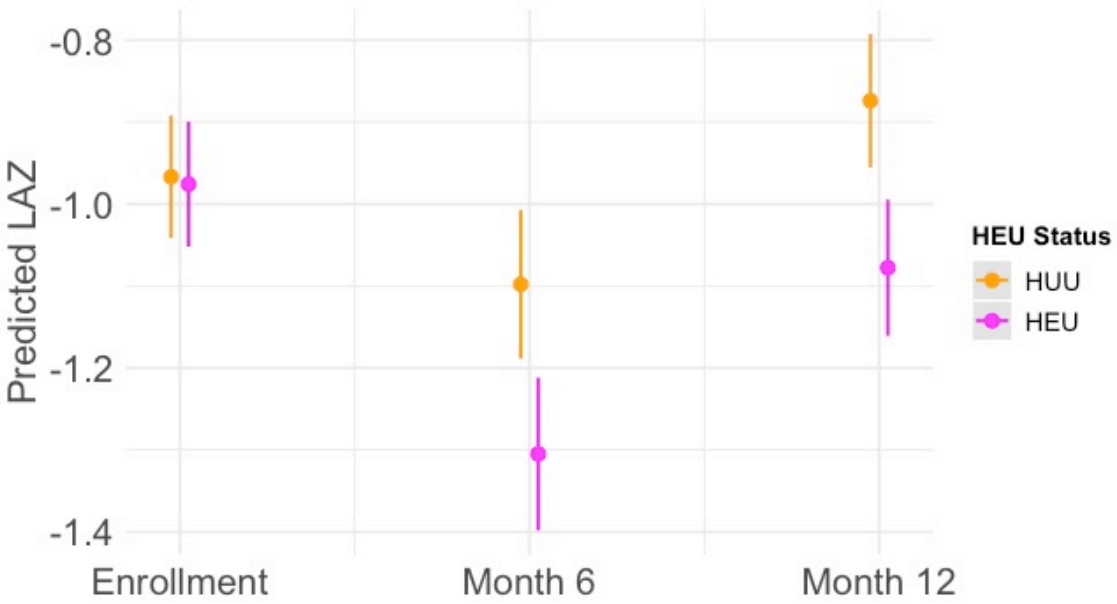


Figure 3. Predicted Regression Estimates and 95% CIs for Interaction Between Visit and HEU Status on Infant LAZ



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