Birth size and early pneumonia predict linear growth among HIV-exposed uninfected infants

Emily L. Deichsel¹ | Patricia B. Pavlinac¹ | Barbra A. Richardson¹ | Dorothy Mbori-Ngacha² | Judd L. Walson^{1,3} | Christine J. McGrath¹ | Carey Farquhar¹ | Rose Bosire⁴ | Elizabeth Maleche-Obimbo⁵ | Grace C. John-Stewart¹

¹ Biostatistics, Global Health, Epidemiology, Medicine, University of Washington, Seattle, Washington

² United Nations Children's Fund (UNICEF), New York, New York

³ Child Acute Illness and Nutrition (CHAIN) Network, Nairobi, Kenya

⁴ Center for Public Health Research, Kenya Medical Research Institute (KEMRI), Nairobi, Kenya

⁵ Department of Paediatrics and Child Health, University of Nairobi, Nairobi, Kenya

Correspondence

Emily L. Deichsel, Biostatistics, Global Health, Epidemiology, Medicine, University of Washington, Box 359909, 325 Ninth Ave, Seattle, WA 98104.
Email: deichsel@uw.edu

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Abstract

Stunting remains a global health priority, particularly in sub-Saharan Africa. Identifying determinants of linear growth in HIV-exposed uninfected (HEU) infants can inform interventions to prevent stunting in this vulnerable population. HIV-infected mothers and their uninfected infants were followed monthly from pregnancy to 12-month post-partum in Nairobi, Kenya. Mixed-effects models estimated the change in length-for-age z-score (LAZ) from birth to 12 months by environmental, maternal, and infant characteristics. Multivariable models included factors univariately associated with LAZ. Among 372 HEU infants, mean LAZ decreased from -0.54 (95% confidence interval [CI] $[-0.67, -0.41]$) to -1.09 (95% CI $[-1.23, -0.96]$) between 0 and 12 months. Declines in LAZ were associated with crowding (≥ 2 persons per room; adjusted difference [AD] in 0–12 month change: -0.46 ; 95% CI $[-0.87, -0.05]$), use of a pit latrine versus a flush toilet (AD: -0.29 ; 95% CI $[-0.57, -0.02]$), and early infant pneumonia (AD: -1.14 ; 95% CI $[-1.99, -0.29]$). Infants with low birthweight ($< 2,500$ g; AD: 1.08 ; 95% CI $[0.40, 1.76]$) and birth stunting (AD: 1.11 ; 95% CI $[0.45, 1.78]$) experienced improved linear growth. By 12 months of age, 46 infants were stunted, of whom 11 (24%) were stunted at birth. Of the 34 infants stunted at birth with an available 12-month LAZ, 68% were not stunted at 12 months. Some low birthweight and birth-stunted HEU infants had significant linear growth recovery. Early infant pneumonia and household environment predicted poor linear growth and may identify a subgroup of HEU infants for whom to provide growth-promoting interventions.

KEYWORDS

HIV exposed uninfected, infant linear growth, Kenya, low birthweight, pneumonia

1 | INTRODUCTION

Stunting (length-for-age z-score [LAZ] < -2), an indicator of chronic undernutrition, is high in sub-Saharan Africa where approximately

36% of children under five are stunted (Black et al., 2013). Poor linear growth is associated with increased infectious disease morbidity and mortality in childhood (Black et al., 2008; Olofin et al., 2013) and combined with undernutrition is an underlying

cause in nearly one third of all childhood deaths globally (Black et al., 2013; Pelletier, Frongillo, Schroeder, & Habicht, 1995). Linear growth faltering, an abnormally slow rate of height gain (measured as decline in LAZ), in the first two years of life is associated with cognitive delays, poor school achievement, and reduced adult work capacity (Adair et al., 2013; Cheung & Ashorn, 2010; Grantham-McGregor et al., 2007; Haas, Murdoch, Rivera, & Martorell, 1996; Kuklina, Ramakrishnan, Stein, Barnhart, & Martorell, 2006; Powell, Walker, Himes, Fletcher, & Grantham-McGregor, 1995; Victora et al., 2008).

The rapid expansion of effective strategies to prevent mother-to-child transmission (PMTCT) of HIV resulted in a growing population of HIV-exposed infants who are born uninfected (HEU) and remain HIV uninfected (Barron et al., 2013; Goga, Dinh, & Jackson, 2012; Joint United Nations Programme on HIV/AIDS (UNAIDS), 2016). In 2016 alone, more than one million HEU infants were born (Slogrove et al., 2018). HEU infants are born with lower birthweight and shorter length compared with HIV-unexposed uninfected infants (Bailey, Kamenga, Nsuami, Nieburg, & St Louis, 1999; Evans, Humphrey, Ntozini, & Prendergast, 2016; Kurewa et al., 2009; Marinda et al., 2007; Patel et al., 2010; Sofeu et al., 2014; Taha et al., 1995) and experience high rates of stunting within the first five years (Bailey et al., 1999; Bobat, Coovadia, Moodley, Coutsooudis, & Gouws, 2001; McGrath et al., 2012; Newell, Borja, & Peckham, 2003; Patel et al., 2010).

Linear growth during infancy is influenced by a multitude of factors. There is an increasing evidence that maternal and early infant factors predict linear growth during infancy (Danaei et al., 2016; MAL-ED Network Investigators, 2017a), with up to 20% of stunting at one year of age originating in the fetal period (Black et al., 2013). Despite decades of investigation on the relationship between childhood infections and malnutrition, there remains controversy over the long-term effect of common early life infections, including diarrhoea and pneumonia, on childhood linear growth (Black et al., 2013; Danaei et al., 2016; de Onis & Branca, 2016; MAL-ED Network Investigators, 2017a; Prendergast & Humphrey, 2014; Schlaudecker, Steinhoff, & Moore, 2011; Victora, de Onis, Hallal, Blössner, & Shrimpton, 2010; Webb, Manji, Fawzi, & Villamor, 2009). Further assessment of prenatal and early life risk factors that are associated with linear growth faltering in vulnerable populations is needed to help identify appropriate interventions to optimize child growth.

Few studies have examined risk factors for poor linear growth among HEU children, a population in whom risk factors for linear growth faltering may be unique. HEU children may have immune consequences due to HIV exposure in utero and during breastfeeding and may be more likely to be exposed to infectious diseases as a consequence of living in a household with one or more HIV-infected individuals (Evans, Jones, & Prendergast, 2016; Ruck, Reikie, Marchant, & Kollmann, 2016; Slogrove et al., 2016). We examined prenatal and early infant predictors of linear growth during the first year of life among HEU infants.

Key messages

- Some infants who are born small (low birthweight or short length) experience significant linear growth recovery by the end of the first year of life.
- Early infant pneumonia and household environment may be markers for future infant linear growth faltering.
- Additional research is needed to understand distinct mechanisms that contribute to linear growth decline and recovery.
- Interventions to improve linear growth among vulnerable populations such as HEU infants will require a multifaceted approach.

2 | METHODS

2.1 | Study design

The parent cohort study has been described elsewhere (Gichuhi et al., 2005; E. M. Obimbo et al., 2004; E. M. Obimbo et al., 2009). Briefly, HIV-infected pregnant women living in Nairobi, Kenya between 1999 and 2002 were enrolled at ≥ 32 weeks of gestation and followed with their infants for 12-month post-partum to assess immunologic mechanisms of protection from breastmilk HIV transmission.

2.2 | Clinical procedures

Risk of HIV-transmission via breastmilk was explained to all women during pregnancy, and they were counselled and supported in their choice to breastfeed or formula feed their infant, including provision of free formula. According to national guidelines during the study period, mothers received short-course zidovudine for PMTCT, and those severely immunocompromised (CD4 count < 200 cells/ μ l) received cotrimoxazole prophylaxis. Neither mothers nor infants received antiretroviral therapy (ART) or prophylaxis during breastfeeding.

Sociodemographic and current and past health information were collected at enrolment with a standardized questionnaire in the study clinic. All participants underwent a comprehensive clinical exam that included anthropometric measurements and blood samples for CD4 count and HIV RNA viral load (VL) tests. Mothers and infants were seen at scheduled clinic visits occurring two weeks post-partum and monthly from birth to 12 months of age. At each clinic study visit, infants underwent a physical examination by study physicians; trained staff measured the infant's weight and recumbent length. Mothers were asked about breastfeeding and their infant's illness in the past month including diarrhoea, assessment for pneumonia, and hospitalizations using standardized questionnaires. Mothers were also encouraged to return to the study clinic if their infant was sick, from which morbidity diagnoses were recorded. To assess infant HIV status, dried blood spots were collected at birth and all subsequent study visits for

HIV DNA detection using polymerase chain reaction for HIV DNA *gag* sequences (Panteleeff et al., 1999).

2.3 | Current analysis

The current analysis included singleton or firstborn twins with documentation of sex, at least one negative HIV polymerase chain reaction confirmatory test and at least two recorded length measurements. Infants were excluded from the analysis if they tested positive for HIV at or before one month of age due to likely perinatal HIV infection. Infants remained in the analysis until the end of follow up (age 12 months) or their last HIV-negative test for those who died, tested HIV polymerase chain reaction positive, or were lost to follow up.

Early life infant morbidity exposures included clinician diagnosis of any diarrhoea or pneumonia using the International Management of Child Illness guidelines or maternal report of hospitalization within the six weeks of life (<42 days).

To reduce potential bias due to missing baseline correlate values, we used Markov chain Monte Carlo procedures to impute missing values assuming an underlying multivariable normal model ($m = 10$ imputations; Sterne et al., 2009). Missing outcome values were not imputed. All correlates in addition to 12-month HIV status, infant sex, infant mortality, and maternal mortality were included in the imputation models. For comparison, we also conducted a complete case analysis. LAZ was calculated using the WHO Anthro software package based on the 2006 WHO Child Growth Standards (WHO Multicentre Growth Reference Study Group, 2006).

Loess curves were used to plot growth over time. We estimated the average LAZ trajectories by environmental, maternal, and infant characteristics using linear spline mixed-effects models with knot points at four and eight months. Knots were selected based on the distribution of data and visual inspection of cohort growth trends. Random effects for the intercept and slope as well as an autocorrelation structure for residual errors were included to account for within-person correlation in the variance estimation. Models included the correlate of interest, spline terms for infant age, and interaction terms between each correlate and age. The multivariable model included correlates associated with LAZ in univariate models (p value < .05). We tested for collinearity using standard error assessments. Predicted LAZ from the univariate mixed-effects models were used to plot growth profiles for correlates included in the multivariable model. We conducted sensitivity analyses to evaluate the influence of error in length measurements. If the difference in length between two consecutive visits indicated a loss in length in centimetres (<0), the LAZ from the previous visit was carried forward to replace the smaller length measurement and the main analysis was replicated using an edited data set. Additionally, we repeated the main analysis in a subset of infants who had survived and remained HIV-negative until 12 months of age to assess survival bias in the main analysis results.

The parent cohort study and current analysis received ethical approval from the Kenyatta National Hospital Ethics and Research Committee and the University of Washington Institutional Review

Board. All analyses were conducted in Stata 14 (StataCorp, College Station, Texas), and $p < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Study population

Overall, 372 singleton or first twins (six twins) born to HIV-positive women in the parent cohort were included in the present analysis (Figure 1). At enrolment, 52% of participants' homes had a pit latrine; 91% had a shared versus household toilet, and 84% of households were considered crowded (defined as ≥ 2 people per room). Median maternal age was 25 years (interquartile range [IQR]: 22–28), and 42% of mothers had more than a primary education. At 32 weeks of gestation (enrolment), 13% of mothers were undernourished (mid-upper arm circumference [MUAC] < 23.5); 8% were severely immunocompromised (CD4 count < 200/ μ l), and 30% had high VL (VL > $\log_{10}$ 5 copies/ml).

Six percent of infants were born with low birthweight (<2,500 g), and 13% were stunted at birth; 15 (4%) infants had both low birthweight and stunting at birth. The majority of infants (75%) received some breastmilk with 29% exclusively breastfed for at least three months. In the first six weeks of life, 3% of infants experienced diarrhoea; 3% were diagnosed with pneumonia, and 7% were hospitalized.

3.2 | Growth patterns

Of the 372 infants, 18 acquired HIV, and 29 died before the end of 12-month follow up and were censored at median 92 (IQR: 30–183) and 90 (IQR: 32–180) days at the last HIV-negative test, respectively. On average, infants experienced a deterioration of LAZ during the first year of life, from -0.54 (95% confidence interval [CI]: $[-0.67, -0.41]$) at birth to -1.09 (95% CI $[-1.23, -0.96]$) at 12 month, with a mean change in LAZ of -0.55 (95% CI $[-0.71, -0.40]$; Figure 2). By one year, 17% (46/269) of children were stunted. Among the 34 infants stunted at birth with available 12-month LAZ, 32% (11) remained stunted at one year,

FIGURE 1 Participant flow chart

FIGURE 2 Scatter plot change in length-for-age z-score over time by infant age. Loess curve represents modest growth decline over first year

whereas 68% (23) were not stunted at 12 months of age. At 12 months, 46 (17%) infants were stunted, of whom 24% (11) were stunted at birth.

3.3 | Correlates of growth

Socio-economic status and sanitation were associated with change in LAZ from birth to 12 months. Infants in homes with pit latrines ($p = .010$), shared toilet ($p = .032$), or crowding ($p = .005$) experienced a greater deterioration of LAZ (Table 1), despite having similar LAZ at birth for pit latrine and household crowding (Figure 3). Of the household sanitation factors, crowding and use of a pit latrine remained significantly associated with greater declines in LAZ in the multivariable analysis ($p = .026$ and $p = .038$, respectively).

Mothers with more than primary education had infants with significantly less deterioration of LAZ ($p < .001$) compared with mothers with less than primary education, even after adjusting for infant birth size, household toilet type, and early infant pneumonia. Greater maternal height ($p = .015$) was associated with gains in LAZ, whereas pregnancy mid-upper arm circumference ($p = .105$) and weight ($p = .14$) were not associated with LAZ. The significant association between infant growth and maternal height also held after adjustment for low birthweight, stunting at birth, and other correlates. Pregnancy CD4 count ($CD4 < 200$: $p = .939$; $CD4 200-499$: $p = .447$) and VL ($p = .455$) were not associated with infant LAZ.

Infants with low birthweight (Figure 3) or stunting at birth had lower LAZ scores for the first year of life relative to their counterparts but experienced gains in linear growth by 12 months (Table 1, both $p < .001$). The associations remained significant in the multivariable analysis for both variables. In a sensitivity analysis of infants surviving and remaining HIV negative to 12 months of age, low birthweight, and stunting at birth remained significantly associated with gains in linear growth (Table A1). Neither any breastfeeding nor exclusive breastfeeding for more than three months were associated with 0–12 month change in LAZ ($p = .099$ and $p = .438$, respectively). Early infant diarrhoea and hospitalization were not associated with changes in LAZ ($p = .488$ and $p = .181$, respectively). Early infant pneumonia was associated with declines in LAZ ($p = .011$), even after adjustment.

Infants with early life pneumonia had lower birth LAZ and continued to have lower LAZ and greater LAZ decline from birth to 12 months than infants without early pneumonia (Figure 3).

Results from the sensitivity analyses without imputed data and corrections in infant length measurement error (Tables A2 and A3) were consistent for the univariate analyses. Whereas the main effects in the multivariable analyses were relatively unchanged, household crowding and low birthweight were no longer significantly associated with change in infant LAZ in either sensitivity analysis, and pit latrine was no longer significant in the length measurement error analysis. The results from sensitivity analysis among infants who survived and remained HIV negative differed slightly from the main analysis (Table A1). In the univariate results, shared toilet and maternal height were no longer associated with infant linear growth; additionally, hospitalization was positively associated with infant change in LAZ, among survivors. These discrepancies could be reflections of the unstable independent associations of these correlates or a result of reduced power in the complete case and survival sensitivity analyses.

4 | DISCUSSION

In this cohort of HEU infants, we assessed early life household, maternal, and infant factors associated with linear growth from birth to 12 months of life. HEU infants with low birthweight or stunting at birth experienced some recovery in linear growth and less linear growth decline compared with normal birthweight and nonstunted infants. Most of the HEU infants who were stunted by 12 months of age were not stunted at birth, underscoring the importance of post-natal factors in growth during the first year of life. Early infant pneumonia was independently associated with persistent declines in length throughout the first year of life, whereas early infant diarrhoea and all-cause hospitalization were not. Higher maternal education and maternal height were protected from linear growth faltering, whereas household crowding and lack of access to flush toilets were associated with linear growth declines.

On average, HEU infants experienced a decline of 0.55 LAZ during the first year. The magnitude of this decline is lower than recent cohorts of HEU children in sub-Saharan Africa noting a -1.00 to -1.50 change in z-score in the first year (Islam et al., 2018; MAL-ED Network Investigators, 2017a; Sudfeld et al., 2017; Webb et al., 2009). Mean LAZ at 12 months in this analysis (-0.96) was half that of the Kenya national average at the same age (-1.80 ; C. G. Victora et al., 2010). This cohort may have had more engagement in health care relative to the general population due to the monthly clinic visits, which included regular counselling on infant nutrition and health, and free infant formula. The prevalence of stunting in the general population increases with age and appears to peak at 24 months of age (Islam et al., 2018; MAL-ED Network Investigators, 2017a; C. G. Victora et al., 2010). Thus, our rates of stunting may be lower because we did not follow children to 24 months during the peak of stunting prevalence.

We noted a strong association between early infant pneumonia and LAZ decline. This relationship persisted after adjusting for socio-

TABLE 1 Change in LAZ scores from 0 to 12 months of 372 Kenyan HEU infants by socio-economic, maternal, and infant factors using linear spline mixed effects models and multiple imputation for missing correlate values

Correlates	N (%) ^a or median IQR	LAZ scores		
		Change 0–12 months ^b	Univariate Difference in change 0–12 months (95% CI) ^b	Multivariable Difference in change 0–12 months (95% CI) ^c
Total		–0.55 ± 0.08		
Home environment factors				
Pit latrine	193 (52%)	–0.74 ± 0.10	–0.40 [–0.71, –0.10]*	–0.29 [–0.57, –0.02]*
Flush toilet	179 (48%)	–0.34 ± 0.12	Ref	Ref
Shared toilet	339 (91%)	–0.61 ± 0.08	–0.50 [–0.95, –0.04]*	–0.20 [–0.66, 0.26]
Household toilet	32 (9%)	–0.11 ± 0.22	Ref	Ref
≥2 persons/room in house	314 (84%)	–0.66 ± 0.08	–0.62 [–1.06, –0.18]*	–0.46 [–0.87, –0.05]*
<2 persons/room in house	55 (15%)	–0.03 ± 0.21	Ref	Ref
Maternal factors				
>Primary education	155 (42%)	–0.17 ± 0.12	0.66 [0.35, 0.97]**	0.44 [0.17, 0.71]*
≤Primary education	213 (57%)	–0.83 ± 0.10	Ref	Ref
Primiparous	279 (75%)	–0.60 ± 0.09	–0.18 [–0.52, 0.16]	
Multiparous	90 (24%)	–0.42 ± 0.15	Ref	
Prepartum anthropometry				
Height (10 cm in models)	160 (157–165)	--	0.29 [0.05, 0.53]*	0.22 [0.00, 0.43]*
Weight (10 kg in models)	63 (58–68)	--	0.13 [–0.03, 0.28]	
MUAC < 23.5	50 (13%)	–0.85 ± 0.20	–0.35 [–0.78, 0.07]	
MUAC ≥ 23.5	244 (66%)	–0.50 ± 0.09	Ref	
Prepartum maternal HIV				
CD4 count <200	28 (8%)	–0.59 ± 0.32	0.03 [–0.65, 0.70]	
CD4 count 200–499	189 (51%)	–0.49 ± 0.17	0.13 [–0.20, 0.45]	
CD4 count >500	147 (40%)	–0.62 ± 0.12	Ref	
Viral load ≥5 log ₁₀ copies/ml	110 (30%)	–0.59 ± 0.09	–0.15 [–0.53, 0.24]	
Viral load <5 log ₁₀ copies/ml	223 (60%)	–0.44 ± 0.17	Ref	
Infant factors				
Birthweight <2,500 g	21 (6%)	1.36 ± 0.39	2.02 [1.23, 2.80]**	1.11 [0.45, 1.78]*
Birthweight ≥2,500 g	343 (92%)	–0.66 ± 0.08	Ref	Ref
Birth LAZ < –2 (stunted)	48 (14%)	0.61 ± 0.20	1.38 [0.95, 1.80]**	1.19 [0.79, 1.59]**
Birth LAZ ≥ –2 (not stunted)	295 (86%)	–0.77 ± 0.08	Ref	Ref
Ever breastfed	279 (75%)	–0.64 ± 0.08	–0.33 [–0.73, 0.06]	
Never breastfed	93 (25%)	–0.31 ± 0.18	Ref	
Exclusively breastfed ≥ first 3 m	107 (29%)	–0.65 ± 0.14	–0.13 [–0.46, 0.20]	
Exclusively breastfed < first 3 m	265 (71%)	–0.52 ± 0.10	Ref	
Infant illness in first month of life				
Diarrhoea	11 (3%)	–0.92 ± 0.53	–0.37 [–1.44, 0.69]	
No Diarrhoea	361 (97%)	–0.54 ± 0.08	Ref	
Pneumonia	13 (3%)	–1.71 ± 0.46	–1.20 [–2.11, –0.28]*	–1.14 [–1.99, –0.29]*
No pneumonia	359 (97%)	–0.51 ± 0.08	Ref	Ref

(Continues)

TABLE 1 (Continued)

Correlates	N (%) ^a or median IQR	LAZ scores		
		Change 0–12 months ^b	Univariate Difference in change 0–12 months (95% CI) ^b	Multivariable Difference in change 0–12 months (95% CI) ^c
Hospitalization	26 (7%)	0.06 ± 0.49	0.66 [−0.31, 1.62]	
No hospitalization	346 (93%)	−0.60 ± 0.08	Ref	

Abbreviations: CI, confidence interval; HEU, HIV-exposed uninfected; IQR, interquartile range; LAZ, length-for-age z-score; MUAC, mid-upper arm circumference.

^aPercents may not add to 100% due to missing data. Missing values were imputed in models; Missing (n): Shared toilet (1), persons/room (3), maternal education (4), parity (3), maternal height (7), maternal weight (5), maternal MUAC (78), maternal CD4 (8), maternal viral load (39), infant birth stunting (29), and infant birthweight (8).

^bEstimated from univariate linear spline regression models and multiple imputation for missing correlate values. 95% CIs were calculated using robust variance estimates.

^cEstimated from multivariable linear spline regression models and multiple imputation for missing correlate values adjusted for pit latrine (vs. flush toilet), shared toilet (vs. household), crowding, maternal education, maternal height, low birthweight, birth-stunting, early infant pneumonia, and age. 95% CIs were calculated using robust variance estimates.

p* value < .05. *p* value < .001.

economic factors, maternal height, low birthweight, and birth stunting. Stunting and acute malnutrition are known to increase the risk for acquisition and severity of pneumonia, (Moschovis et al., 2015; Schlaudecker et al., 2011) and although historical studies have shown an association between pneumonia and other respiratory infections and length gains in children age 9–36 months, (Victora, Barros, Kirkwood, & Vaughan, 1990; Walker, Grantham-McGregor, Powell, Himes, & Simeon, 1992) recent studies in older children have not detected an association between respiratory illness and linear growth (MAL-ED Network Investigators, 2017a; Webb et al., 2009). Early infant pneumonia may be more likely to occur in vulnerable children, including HEU infants, with reduced quantity and function of passively acquired maternal antibodies (Abu-Raya, Smolen, Willems, Kollmann, & Marchant, 2016). Pneumonia infection in the first month of life may identify infants with a declining linear growth trajectory influenced either by prenatal factors or their postnatal environment.

We expected that diarrhoea early in life would be associated with linear growth faltering (Checkley, Epstein, Gilman, Cabrera, & Black, 2003; Richard et al., 2013; Scrimshaw, 1970; Venkatesh et al., 2010). However, unlike pneumonia, we did not observe an association between early infant diarrhoea and poor linear growth. Effects of diarrhoea on growth may depend on burden or severity of diarrhoea over the first year of life. Recent evidence suggests that infections with specific enteric pathogens may be responsible for linear growth faltering independent of symptomatic diarrhoea (MAL-ED Network Investigators, 2017b; Rogawski et al., 2018; Schnee et al., 2018).

Infants with low birthweight or stunting at birth had lower LAZ throughout follow up than their counterparts. However, surviving HIV-uninfected infants with low birthweight or short birth length caught up in their LAZ, nearly returning to the levels of their non-low birthweight and birth-stunted counterparts by 12 months of age, consistent with other studies (Webb et al., 2009). Low birthweight has been identified as a mediator of the relationship of HIV exposure and stunting (Sudfeld et al., 2016) and as much as 20% of stunting in

the first year of life has been attributed to fetal growth restriction (Black et al., 2013; Christian et al., 2013). We found that almost a third (28%) of infants stunted at 12 months were stunted at birth, suggesting an appreciable impact of fetal growth on long-term stunting. There is some evidence that maternal ART or specific antiretroviral drugs may increase the risk of preterm birth and early stunting in HEU infants (Hofer et al., 2016; Powis et al., 2016; Strydom, Nel, Dhansay, & Van, 2018). As ART continues to be more widely used and the population of HEU children continues to grow, the relative contribution of ART-associated linear growth faltering in the overall prevalence of stunting may be appreciable. With the WHO guidelines recommending lifelong ART among all HIV-infected individuals, including HIV-infected pregnant women, it will be important to identify factors associated with linear growth in the context of longer maternal ART exposure and specific drug regimens.

We found that infants born to mothers with more than primary education or of taller stature experienced less linear growth decline compared with those with less educated and shorter mothers. Maternal education is consistently associated with improved childhood growth in SSA (Omoni et al., 2017; Webb et al., 2009). Among HIV-infected mothers, those with more schooling may have greater knowledge regarding health care seeking, and adherence to medical advice, each of which may help to protect the health of the mother and her infant. Taller maternal stature suggests that linear growth is, in part, informed by genetic potential. This association could also suggest the intergenerational causes of stunting where a mother, stunted since childhood, gives birth to a stunted baby, indicating mother's childhood environment and nutrition contributes to the growth trajectory of her future infant (Black et al., 2013; Martorell & Zongrone, 2012; Prendergast & Humphrey, 2014).

We noted associations between household toilet type and crowding with decline of LAZ. Pit latrines, shared toilets, and household crowding represent contaminated environments and exposure to infectious pathogens that may contribute to growth decline. They

FIGURE 3 Mean predicted length-for-age z-score (LAZ; line) and 95% confidence intervals (grey) over the first year of life for exposure (—) and (– –) reference groups of correlates included in multivariable model. P values for difference in change in LAZ from 0 to 12 months from univariate models.

also may represent low socio-economic status, limited resources, and agency to access necessary health care and nutrient rich foods to prevent and treat infections and malnutrition. Because of the complex relationships between these contributing factors, childhood malnutrition and stunting has been difficult to prevent and treat. Targeted interventions to improve household or community sanitation and hygiene have not demonstrated consistent improvement in linear growth (Luby et al., 2018; Null et al., 2018). However, evidence from Brazil suggests broad multisectoral interventions to promote access to and use of health care services as well as household financial

stability decreased the prevalence of stunting nationwide (Rasella et al., 2018).

There are limitations to our study. First, the cohort experienced less stunting and had higher 12-month LAZ than anticipated, which decreased statistical power to detect modest associations. Additionally, limited statistical power may explain the lack of significant association of LAZ change with hospitalization and diarrhoea in early infancy. Second, not all infants had length measurements at each of the 12 follow up visits; however, the mixed-effects model addresses interval missingness of the outcome variable by evaluating associations up until

the time of censoring. Third, regression to the mean, caused by measurement error, could partially explain the finding that infants born extremely small tend to have more gains in LAZ. We evaluated the possible effect of regression to the mean by rerunning the low birthweight and birth stunting analyses with and without adjustment for the difference between the individual's LAZ value and the group mean LAZ value at enrolment (Barnett, van der Pols, & Dobson, 2005) and found minimal differences in the univariate and adjusted results. Fourth, we did not have an HIV-unexposed comparison group; it is possible that our findings may reflect vulnerable infants in this region in general, not solely HEU. Finally, the cohort received short-course antiretrovirals rather than current Option B+ PMTCT regimens. Although this enabled determination of the influence of maternal immune and viral levels on infant growth, we did not find associations between maternal immune status or VL on growth outcomes suggesting that studies in virally suppressed Option B+ HEU cohorts could yield similar predictors. Nonetheless, the predictors are potentially important in HEU, and perhaps more widely.

In summary, we found that although low birthweight infants and infants stunted at birth had linear growth recovery in the first year of life, early infant pneumonia and household sanitation had sustained effects on linear growth trajectory. There are likely distinct mechanisms by which prebirth and postbirth factors contribute to linear growth recovery or decline. Interventions to improve linear growth among HEU infants require a multifaceted approach, including improvement of sanitation, maternal education, and prevention of early life infant infections, to address a variety of mechanisms causing linear growth faltering in vulnerable populations.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONTRIBUTIONS

ELD, GCJ-S, PBP, JLW, CF, BAR, and CJM conceived and designed the study; GCJ-S, DM-N, EM-O, and RB collected the data; ELD and BAR performed statistical analysis, and ELD, GCJ-S, and PBP drafted the manuscript. All authors contributed to data interpretation and critical revision of the manuscript for intellectual content. All authors read and approved the final manuscript.

ORCID

Emily L. Deichsel <https://orcid.org/0000-0002-6172-9458>

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APPENDIX A

TABLE A1 Correlates of 0- to 12-month change in LAZ scores of 330 Kenyan HEU infants surviving HIV uninfected through 12 months of age using linear spline mixed-effects models and multiple imputation for missing correlate values

		Univariate	Multivariable model
Cofactors	N (%) ^a or median IQR	Difference in change 0–12 months (95% CI) ^b	Difference in change 0–12 months (95% CI) ^c
Home environment factors			
Pit latrine	173 (52%)	−0.43 [−0.73, −0.13]*	−0.34 [−0.62, −0.07] [†]
Flush toilet	157 (48%)	Ref	Ref
Shared toilet	298 (90%)	−0.39 [−0.85, 0.07]	−0.13 [−0.59, 0.34]
Household toilet	31 (9%)	Ref	Ref
≥2 persons/room in house	277 (84%)	−0.63 [−1.07, −0.18]*	−0.54 [−0.95, −0.12]*
<2 persons/room in house	50 (15%)	Ref	Ref
Maternal factors			
>Primary education	140 (42%)	0.56 [0.25, 0.87]**	0.38 [0.10, 0.65]*
≤Primary education	186 (56%)	Ref	Ref
Primiparous	242 (73%)	−0.10 [−0.44, 0.25]	
Multiparous	86 (26%)	Ref	
Prepartum anthropometry			
Height (10 cm in models)	160 (157, 165)	0.23 [−0.01, 0.47]	0.17 [−0.03, 0.36]
Weight (10 kg in models)	63 (58, 68)	0.10 [−0.07, 0.27]	
MUAC < 23.5	40 (12%)	−0.25 [−0.68, 0.19]	
MUAC ≥ 23.5	224 (68%)	Ref	
Prepartum maternal HIV			
CD4 count < 200	21 (6%)	−0.04 [−0.71, 0.63]	
CD4 count 200–499	171 (52%)	0.10 [−0.22, 0.42]	
CD4 count > 500	132 (40%)	Ref	
Viral load ≥ 5 log ₁₀ copies/ml	88 (27%)	−0.09 [−0.48, 0.30]	
Viral load < 5 log ₁₀ copies/ml	208 (63%)	Ref	
Infant factors			
Birthweight < 2,500 g	15 (5%)	1.94 [1.03, 2.85]**	1.16 [0.38, 1.93]*
Birthweight ≥ 2,500 g	308 (93%)	Ref	Ref
Birth LAZ < −2 (stunted)	42 (13%)	1.29 [0.85, 1.73]**	1.11 [0.71, 1.52]**
Birth LAZ ≥ −2 (not stunted)	260 (79%)	Ref	Ref
Ever breastfed	247 (75%)	−0.46 [−0.84, −0.08]*	
Never breastfed	83 (25%)	Ref	
Exclusively breastfed ≥3 months	94 (28%)	−0.16 [−0.48, 0.17]	
Exclusively breastfed <3 months	236 (72%)	Ref	
Infant illness in first month of life			
Diarrhoea	14 (4%)	−0.37 [−1.43, 0.69]	
No Diarrhoea	316 (96%)	Ref	
Pneumonia	9 (3%)	−0.77 [−1.37, −0.16]*	−0.83 [−1.45, −0.22]*
No pneumonia	321 (97%)	Ref	Ref

(Continues)

TABLE A1 (Continued)

Cofactors	N (%) ^a or median IQR	Univariate	Multivariable model
		Difference in change 0–12 months (95% CI) ^b	Difference in change 0–12 months (95% CI) ^c
Hospitalization	20 (6%)	0.92 [0.09, 1.74]*	
No hospitalization	310 (94%)	Ref	

Abbreviations: CI, confidence interval; HEU, HIV-exposed uninfected; IQR, interquartile range; LAZ, length-for-age z-score; MUAC, mid-upper arm circumference.

^aPercents may not add to 100% due to missing data; missing (n): shared toilet (1), persons/room (3), maternal education (4), parity (2), maternal height (7), maternal weight (5), maternal MUAC (66), maternal CD4 (6), maternal viral load (34), infant birth stunting, (28), and infant birthweight (7).

^bEstimated from univariate linear spline regression models and multiple imputation for missing correlate values, 95% CIs were calculated using robust variance estimates.

^cEstimated from multivariable linear spline regression models and multiple imputation for missing correlate values adjusted for pit latrine (vs. flush toilet), shared toilet (vs. household), crowding, maternal education, maternal height, low birthweight, birth stunting, early infant pneumonia, and age, 95% CIs were calculated using robust variance estimates.

p* value < .05. *p* value < .001.

TABLE A2 Complete case sensitivity analysis, correlates of 0- to 12-month change in LAZ scores among 372 HEU infants using linear spline mixed-effects models

Cofactors	Complete case analysis	
	Univariate Difference in change 0–12 months (95% CI) ^a	Multivariable model Difference in change 0–12 months (95% CI) ^b
Home environment factors		
Pit latrine	−0.42 [−0.72, −0.11]*	−0.25 [−0.53, 0.04]
Flush toilet	Ref	Ref
Shared toilet	−0.50 [−0.95, −0.04]*	−0.26 [−0.74, 0.22]
Household toilet	Ref	Ref
≥2 persons/room in house	−0.65 [−1.09, −0.21]*	−0.38 [−0.79, 0.03]
<2 persons/room in house	Ref	Ref
Maternal factors		
>Primary education	0.69 [0.38, 0.99]**	0.42 [0.14, 0.71]*
≤Primary education	Ref	Ref
Primiparous	−0.16 [−0.51, 0.19]	
Multiparous	Ref	
Prepartum anthropometry		
Height (10 cm in models)	0.29 [0.06, 0.52]*	0.25 [0.04, 0.47]*
Weight (10 kg in models)	0.13 [−0.04, 0.30]	
MUAC < 23.5	−0.44 [−0.90, 0.03]	
MUAC ≥ 23.5	Ref	
Prepartum maternal HIV		
CD4 count < 200	0.01 [−0.67, 0.68]	
CD4 count 200–499	0.13 [−0.19, 0.45]	
CD4 count > 500	Ref	
Viral load ≥ 5 log ₁₀ copies/ml	−0.18 [−0.57, 0.22]	
Viral load < 5 log ₁₀ copies/ml	Ref	

(Continues)

TABLE A2 (Continued)

Cofactors	Complete case analysis	
	Univariate Difference in change 0–12 months (95% CI) ^a	Multivariable model Difference in change 0–12 months (95% CI) ^b
Infant factors		
Birthweight < 2,500 g	2.04 [1.25, 2.83]**	0.44 [−0.14, 1.03]
Birthweight ≥ 2,500 g	Ref	Ref
Birth LAZ < −2 (stunted)	1.61 [1.15, 2.07]**	1.41 [0.99, 1.83]**
Birth LAZ ≥ −2 (not stunted)		
Ever breastfed	−0.34 [−0.73, 0.06]	
Never breastfed	Ref	
Exclusively breastfed ≥3 Mon	−0.13 [−0.45, 0.19]	
Exclusively breastfed <3 Mon	Ref	
Infant illness in first month of life		
Diarrhoea	−0.40 [−1.49, 0.69]	
No Diarrhoea	Ref	
Pneumonia	−1.22 [−2.15, −0.28]*	−1.35 [−2.29, −0.41]*
No pneumonia	Ref	Ref
Hospitalization	0.65 [−0.33, 1.62]	
No hospitalization	Ref	

Abbreviations: CI, confidence interval; HEU, HIV-exposed uninfected; LAZ, length-for-age z-score; MUAC, mid-upper arm circumference.

^aSample size for complete case univariate models: pit latrine (372), shared toilet (371), persons/room (369), maternal education (368), parity (369), maternal height (365), maternal weight (367), maternal MUAC (294), maternal CD4 (364), maternal viral load (333), infant birthweight (364), birth LAZ (343), ever breastfed (372), exclusively breastfed (372), diarrhoea, pneumonia (372), and hospitalization (372).

^bFrom multivariable linear spline models adjusted for pit latrine (vs. flush toilet), shared toilet (vs. household), crowding, maternal education, maternal height, low birthweight, birth-stunting, pneumonia in first month, and age, 95% CIs were calculated using robust variance estimates. Model includes 338 participants.

p* value < .05. *p* value < .001.

TABLE A3 Sensitivity analysis for length measurement error, correlates of 0- to 12-month change in LAZ scores using linear spline mixed effects models in an edited dataset imputed for missing correlate values for 372 HEU infants

Correlate	Univariate Difference in change 0–12 months (95% CI) ^a	Multivariable model Difference in change 0–12 months (95% CI) ^b
Home environment factors		
Pit latrine	−0.36 [−0.68, −0.04]*	−0.22 [−0.51, 0.07]
Flush toilet	Ref	Ref
Shared toilet	−0.47 [−0.93, −0.02]*	−0.27 [−0.74, 0.21]
Household toilet	Ref	Ref
≥2 persons/room in house	−0.53 [−0.98, −0.09]*	−0.40 [−0.82, 0.02]
<2 persons/room in house	Ref	Ref
Maternal factors		
>Primary education	0.59 [0.27, 0.92]**	0.39 [0.10, 0.67]*
≤Primary education	Ref	Ref
Primiparous	−0.26 [−0.61, 0.09]	
Multiparous	Ref	
Prepartum anthropometry		
Height (10 cm in models)	0.36 [0.11, 0.61]*	0.30 [0.08, 0.52]*

(Continues)

TABLE A3 (Continued)

Correlate	Univariate Difference in change 0–12 months (95% CI) ^a	Multivariable model Difference in change 0–12 months (95% CI) ^b
Weight (10 kg in models)	0.13 [–0.05, 0.31]	
MUAC < 23.5	–0.28 [–0.69, 0.13]	
MUAC ≥ 23.5	Ref	
Prepartum maternal HIV		
CD4 count < 200	–0.14 [–0.82, 0.53]	
CD4 count 200–499	0.12 [–0.22, 0.46]	
CD4 count > 500	Ref	
Viral load ≥ 5 log ₁₀ copies/ml	–0.12 [–0.54, 0.29]	
Viral load < 5 log ₁₀ copies/ml	Ref	
Infant factors		
Birthweight < 2,500 g	1.85 [0.95, 2.74]**	0.84 [0.11, 1.57]*
Birthweight ≥ 2,500 g	Ref	Ref
Birth LAZ < –2 (stunted)	1.61 [1.18, 2.03]**	1.49 [1.07, 1.90]**
Birth LAZ ≥ –2 (not stunted)	Ref	Ref
Ever breastfed	–0.26 [–0.68, 0.15]	
Never breastfed	Ref	
Exclusively breastfed ≥ 3 months	–0.06 [–0.40, 0.27]	
Exclusively breastfed < 3 months	Ref	
Infant illness in first month of life		
Diarrhoea	–0.45 [–1.52, 0.63]	
No Diarrhoea	Ref	
Pneumonia	–0.98 [–2.05, 0.10]	–0.90 [–1.91, 0.11]
No pneumonia	Ref	Ref
Hospitalization	0.69 [–0.34, 1.71]	
No hospitalization	Ref	

Note. If the difference in length between two consecutive visits indicate a loss in length in centimetres (<0), the LAZ from the previous visit was carried forward to replace the LAZ of the smaller length measurement, and the main analysis was replicated using an edited data set.

Abbreviations: CI, confidence interval; HEU, HIV-exposed uninfected; LAZ, length-for-age z-score; MUAC, mid-upper arm circumference.

^aEstimated from univariate linear spline regression models and multiple imputation for missing correlate values. 95% CI were calculated using robust variance estimates.

^bEstimated from multivariable linear spline regression models and multiple imputation for missing correlate values adjusted for pit latrine (vs. flush toilet), shared toilet (vs. household), crowding, maternal education, maternal height, low birthweight, birth-stunting, early infant pneumonia, age. 95% CI were calculated using robust variance estimates.

p* value < .05. *p* value < .001.