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Growth patterns and their contributing factors among HIV-exposed uninfected infants

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Abstract

With expanded HIV treatment and prevention programmes, most infants born to HIV-positive women are uninfected, but the patterns and determinants of their growth are not well described. This study aimed to assess growth patterns in a cohort of HIV-exposed uninfected (HEU) infants who participated in an experimental HIV vaccine trial and to test for associations with maternal and infant factors, including in-utero exposure to antiretroviral therapy (ART), mode of delivery, exclusive breastfeeding, mother's education and receipt of the vaccine. Infants in the trial were seen at regular clinic visits from birth to 48 weeks of age. From the anthropometric measurements at these visits, weight-for-age *z*-scores (WAZ), weight-for-length *z*-scores (WLZ) and length-for-age *z*-scores (LAZ) were computed using World Health Organization (WHO) software and reference tables. Growth patterns were investigated with respect to maternal and infant factors, using linear mixed regression models. From 94 infants included at birth, growth data were available for 75.5% at 48 weeks. The determinants of infant growth in this population are multifactorial: infant LAZ during the first year was significantly lower among infants delivered by caesarean section ($p = 0.043$); both WAZ and LAZ were depressed among infants with longer exposure to maternal ART (WAZ: $p = 0.015$; LAZ: $p < 0.0001$) and among infants of mothers with lower educational level (WAZ: $p = 0.038$; LAZ: $p < 0.0001$); the effect of maternal education was modified by breastfeeding practice, with no differences seen in exclusively breastfed infants. These findings inform intervention strategies to preserve growth in this vulnerable infant population.

KEYWORDS

ART, HIV, infant growth, length-for-age, predictors, pregnancy, weight-for-age

1 | INTRODUCTION

The Joint United Nations Programme on HIV and AIDS (UNAIDS) estimated in 2018 that 1.3 million pregnant women were living with HIV, of whom 82% had received antiretroviral (ARV) drugs to prevent mother-to-child transmission (MTCT). In the same year, the estimated number of newly infected children (<15 years) was 160,000, corresponding to a decline of 41% from the 2010 estimate of 280,000 (UNAIDS estimates, 2019).

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With decreased MTCT, the population of HIV-exposed uninfected (HEU) infants has increased (Makasa et al., 2007, Jones et al., 2011, McDonald et al., 2012, McGrath et al., 2012, Sofeu et al., 2014) due to a high coverage of infected women with access to ARV therapy (ART). The majority of HEU infants are born in areas with resource limitations (UNAIDS, 2013). Health vulnerability among the HEU infants has been suggested (Owor et al., 2013), but mechanisms for vulnerability are unclear (Heidari et al., 2011). Wide provision of ART with Option B + prevention of mother-to-child transmisson (PMTCT) implementation has resulted in more HEU infants being exposed to maternal ART in utero and throughout breastfeeding, which, in turn, may influence growth and development of these infants (Briand et al., 2006; Evans, Jones, & Prendergast, 2016).

There have been reports of the effect of maternal HIV infection on both fetal and postnatal growth (Sofeu et al., 2014). Factors potentially affecting growth of HEU infants include demographic and socioeconomic factors (e.g., rural or urban residence, access to clean water and good nutrition), maternal factors (e.g., age, educational level, health status and ART) and infant factors (e.g., birthweight, gender, and episodes of malaria, diarrhoea and respiratory tract infections) (Arpadi et al., 2009; Muhangi et al., 2013).

Studies examining postpartum growth of HEU infants have yielded inconsistent results (Makasa et al., 2007; McDonald et al., 2012; McGrath et al., 2012; Muhangi et al., 2013). Some studies have reported no difference between HEU infants' birthweight and early growth compared with their nonexposed counterparts (Bailey, Kamenga, Nsuami, Nieburg, & St Louis, 1999; Lepage et al., 1996), but others have reported lower birthweights and/or poorer early growth among HEU infants (Makasa et al., 2007; Moye et al., 1996; Sofeu et al., 2014). The inconsistency in findings might be due to methodological issues of anthropometrical studies, such as the selection of a reference group when assessing growth among HEU infants (Makasa et al., 2007) or omission of important growth-related factors (Sofeu et al., 2014).

The aim of our study were to assess growth within a cohort of HEU infants in Kenya who participated in a randomized trial of a candidate HIV vaccine and to determine factors potentially associated with growth differences in this cohort.

Key messages

- Understanding determinants of the growth pattern over time in HIV-exposed uninfected infants informs efforts to preserve the health of these vulnerable children.
- Factors associated with depressed growth in the first year of life included lower maternal education level, longer in-utero exposure to maternal antiretrovirals and delivery by caesarean section.
- The adverse effect of low education was modified by breastfeeding practice, with a significant gap in growth found only for infants not exclusively breastfed according to World Health Organization (WHO) recommendations.
- Monitoring of infant growth outcomes is an important component in the evaluation of expanded prevention of mother-to-child transmission (PMTCT) programmes.

2 | METHODS

This study was nested within a Phase I/II clinical trial, conducted in Nairobi in 2010 to evaluate safety and immunogenicity of a candidate boost HIV-1 vaccine MVA.HIVA (Njuguna et al., 2014). The vaccine was administered to a randomized group of healthy infants born to HIV-infected mothers who had been enrolled during the second or third trimester of pregnancy and followed up at the Kenyatta National Hospital (KNH), where HIV testing and counselling were offered through established PMTCT programmes. Eligible women were those aged 18 or older, who were willing to receive combination ART during pregnancy and breastfeeding (if applicable), intending to deliver at KNH and to remain in the Nairobi area for at least 1 year after delivery. Women were excluded if they had multiple gestation, Stage 3 or 4 HIV according to World Health Organization (WHO) criteria, CD4 counts lower than 350 cells per microlitre, had previously participated in any HIV vaccine trial or received any investigational agent during the pregnancy, or were deemed by the study clinician to have clinically significant disease that would compromise their ability to complete the study. Women were screened for eligibility the first time they were seen during pregnancy and returned to be enrolled, typically 1–2 weeks later.

Infants of eligible women were enrolled during the first 3 days of life if they were considered healthy by the study physician and had a birthweight of ≥2,500 g. Infants who met all inclusion criteria and none of the exclusion criteria were randomized to MVA.HIVA or no intervention at 20 weeks of age. Details of the eligibility criteria, the vaccine and its administration, and information regarding participant follow-up and safety monitoring were previously reported (Njuguna et al., 2014).

2.1 | Outcome measures

Infants had their weight and length recorded together with several related variables at 10 study visits up to 12 months of age: at Weeks 2, 6, 10, 14, 19, 20 (randomization), 21, 28, 36 and 48. The collected data on weight, height, gender and age (in days) were used to calculate weight-for-age *z*-scores (WAZ), length-for-age *z*-scores (LAZ) and weight-for-length *z*-scores (WLZ) using the reference data from the WHO Multicentre Growth Reference Study (WHO growth standards 2006). The reference tables for mid-upper arm circumference (MUAC) start at 3 months of age, so we calculated the *z*-score at all visits from week 14. We assessed

the proportion of wasted, stunted and underweight children according to WHO guidelines (WHO Multicentre Growth Reference Study Group [MGRS], 2006): a WLZ, LAZ or WAZ, respectively, of more than 2 standard deviations below the median for the reference population. We checked the validity of the wasting assessment using mid-upper-arm circumference since this growth indicator is considered in many studies as a reliable indicator of severe wasting among children under 5 years and even as a predictor of child mortality (Bliss et al., 2018).

2.2 | Investigated exposures

In line with the WHO Option B guidelines (WHO advice 2010 ARV use) current at the time of the trial (superseded by new guidelines [WHO consolidated guidelines ARV, 2013] in 2013), all mothers were prescribed ART for PMTCT during the study. Whether or not they were already on ART at the time of screening, women were referred to the antenatal clinic at KNH for prescription and monitoring of ART during pregnancy. All mothers in our study received ART with the following regimens: zidovudine (ZDV) or tenofovir (TDF), lamivudine (3TC), plus lopinavir/ritonavir (LPV/RTV) or efavirenz (EFV) or nevirapine (NVP). All infants received nevirapine (NVP) prophylaxis for the first 6 weeks of life. Furthermore, the antibiotic co-trimoxazole was provided to all infants from 6 weeks of age: formula-fed infants stopped co-trimoxazole at 10 weeks of age if the 6-week HIV-DNA test was negative and breastfed infants continued throughout the breastfeeding period. We defined infants as having a longer in-utero exposure to ART if the mothers reported already being on ART at their screening visit. The reference group (shorter exposure to ART) consisted of the infants of mothers who were on monotherapy or not on any ARVs at screening, all of whom initiated ART at the clinic visit, which was scheduled 1–2 weeks later. For six mothers, it was unclear if they were on ART at screening: we did not exclude the infants of these mothers from analysis, but chose instead to assign them to the reference group in order to have a more conservative analysis. A sensitivity analysis was conducted, excluding the infants of these six women.

Feeding counselling was provided at each study visit, and formula was provided for those who chose formula feeding. Feeding practice at each visit was classified as formula, exclusive breastfeeding or mixed feeding. At each visit up to 6 months of age, we compared infants who had been exclusively breastfed up to that time point to infants who had received any formula or other foods: infants who were exclusively breastfed up to 6 months were considered to have been breastfed according to WHO recommendations (WHO Global strategy for infant and young children feeding 2003) and remained in the 'exclusively breastfed' category for the remainder of follow-up.

For visits following randomization at 20 weeks, exposure to the vaccine was a dichotomous variable with the nonvaccinated infants serving as the reference group. Women were classified by their level of education (higher and lower than secondary level) and the infants by their mode of delivery (vaginal and caesarean).

2.3 | Statistical methods

Connected scatter plots of WAZ and LAZ profiles were prepared for individual infants, and the whole cohort was compared to the WHO references by plotting the mean *z*-scores over time with their upper and lower quartiles. Individual *z*-scores at each visit were assessed using linear models where the nonlinear growth pattern was accommodated by using a piecewise linear spline with knots chosen at 10 and 21 weeks: representing the timing of co-trimoxazole discontinuation and MVA.HIVA vaccination, respectively. We first obtained crude estimates of the effect of each exposure of interest from a simple mixed model, where in addition to the knots, we included only the exposure as a fixed effect, and the intercept as a random effect to allow for different starting values for each child. Adjusted estimates were obtained from a multivariate model where the fixed effects included all characteristics of interest. In addition to possible interactions between the exposures, we also explored interactions between exposure and the linear splines to investigate if there was evidence of different slopes after some children stopped co-trimoxazole (10 weeks) and after most had stopped breastfeeding (21 weeks). The chosen covariance structure for the random effects was 'unstructured' because the anthropometric measurements were recorded at visits separated by unequal time intervals. A significance level of $p < 0.05$ or a 95% confidence interval excluding zero was considered as statistically significant. Descriptive and graphical analysis was conducted using R version 3.4.1 (http://www.r-project.org), with *z*-scores calculated using the WHO reference tables and *igrowup* command in STATA (WHO Anthro, 2011). For the regression models, we used the *mixed* command in STATA version 13 (StataCorp, College Station, TX, USA).

2.4 | Ethical considerations

The study was nested within the PedVacc 002 clinical trial (NCT00981695), approved by the KNH/University of Nairobi Research Ethics Committee (ref. P266/10/2008), Oxford Tropical Research Ethics Committee (ref. OXTREC 52–08), University of Washington Institutional review Board (ref. HSD 35079) and the Stockholm Regional Ethics Committee (ref. 2009/1591–31/1).

3 | RESULTS

A summary of the population and follow-up for this study is provided in Figure S1. A total of 102 mothers were screened and enrolled during pregnancy and were seen at clinic with their infants following delivery. For the 94 infants considered eligible at birth, Table 1 presents the characteristics of their mothers at the screening visit, these infants at the first clinic visit (1–2 weeks) and the characteristics of the infants seen at the randomization visit (Week 20) and at the 1-year follow-up.

The median maternal age at screening was 27 years (interquartile range [IQR]: 23–31), and approximately 22% of these mothers had

TABLE 1 Characteristics of infants who were seen at first study visit following enrolment and their mothers at screening/delivery

Mothers at Visit 1 (*N* = 94)			
Median age in years (IQR)		**27 (23–31)**	
Level of education			
Primary school		40 (42.6%)	
Secondary school		33 (35.1%)	
>Secondary school		21 (22.3%)	
Median CD4-count: Cells per μl (IQR)		543.5 (445.5–653)	
Mean haemoglobin (SD)		11.67 (1.5)	
Median gestational age in weeks (IQR)			
At screening		28 (24–32)	
At clinic visit		29 (24–32)	
At delivery		38 (37–39)	
Ever taken antiretrovirals (ARVs) before screening		62 (66.0%)	
On ARVs at screening		56 (59.6%)	
On ART at screening		37 (39.4%)	
On ART at delivery		93 (98.9%)	
Multiparous		67 (71.3%)	
Any other child tested HIV positive		7/91 (7.7%)	
Delivery method			
Spontaneous vaginal delivery (SVD)		66 (70.2%)	
Elective caesarean		12 (12.8%)	
Emergency caesarean section		16 (17.0%)	
Infants			
	Week 2 visit (*N* = 94)	Randomization visit (*N* = 82)	Final follow-up visit (*N* = 71)
Male	43 (45.7%)	38 (46.9%)	31 (43.7%)
Female	51 (54.3%)	43 (53.1%)	40 (56.3%)
Mean age in weeks (SD)	1.92 (.31)	20.05 (.42)	47.82 (.82)
Feeding practice			
Exclusive breastfeeding	79 (84.0%)	63 (77.8%)	2 (2.8%)
Mixed feeding	0	2 (2.5%)	42 (59.2%)
Formula feeding	15 (16.0%)	16 (19.8%)	27 (38.0%)
Anthropometry			
Mean length, cm (SD)	50.81 (2.05)	62.2 (2.03)	70.66 (2.79)
Mean weight, kg (SD)	3.44 (.43)	6.68 (.97)	8.25 (1.02)
Mean upper arm circumference, cm (SD)	11.37 (1.2)	14.68 (1.30)	15.11 (1.20)
z-Scores			
Underweight (WAZ < −2), *n* (%)	3 (3.2%)	6 (7.4%)	10 (14.1%)
Stunted (LAZ < −2), *n* (%)	4 (4.3%)	13 (16.1%)	20 (28.2%)
Wasted (WLZ < −2), *n* (%)	8 (8.7%)	3 (3.7%)	5 (7.0%)

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; IQR, interquartile range; LAZ, length-for-age *z*-score; WAZ, weight-for-age *z*-score; WLZ, weight-for-length *z*-score.

reached an educational level higher than secondary school. More than 70% of mothers had previously borne children, and seven had a prior child with HIV infection. One-third of the mothers delivered by caesarean section. At the screening visit, median gestational age was 28 weeks (IQR: 24–32), and approximately two-thirds of the mothers (*n* = 62, 65.96%) reported having previously taken ARV medication. At the time of the visit, 56 mothers (59.6%) were on ARVs: 37 (39.36%) on ART and the remainder on monotherapy. All mothers were documented to be on ART at delivery, with the exception of one for whom ART information was missing. The median birthweight of infants was 3,100 g (IQR: 2,900–3,400). Forty six percent of the infants were male, and most infants (84%) were exclusively breastfeeding at the

time of the first clinic visit (1–2 weeks), and 77.8% were still exclusively breastfeeding at 20 weeks of age. Of the 94 infants enrolled at the first visit, 82 (87%) attended the clinic visit at 20 weeks (one had died, and 11 were withdrawn). Of these, 73 were randomized (36 to vaccine and 37 to no treatment) of whom 71 attended their 1-year follow-up visit. Of the nine children not eligible for randomization, one was HIV-infected, eight had health problems, and the mother of one child was unwilling to proceed.

At the first visit after birth, mean WAZ, WLZ and LAZ were −0.57, −0.34 and −0.7, respectively, and growth data were available for 75.5% at 48 weeks. Relative to WHO reference charts, between 3% and 9% of infants in our study had *z*-scores below −2 at their first visit (2 weeks), and this percentage increased at subsequent visits for all three *z*-scores (WAZ, LAZ and WLZ), with 16% LAZ below −2 at 20 weeks and almost 30% at 1 year (Table 1). Only two infants had evidence of severe wasting as defined by MUAC: one at 36 weeks of age (Z = −1.9) and the other at 48 weeks (Z = −2.03). The mean *z*-scores for all infants were consistently below 0 but not below −2 (Figure S2). Male and female infants had similar WAZ, but males had lower LAZ (Figure 1a). The mean WAZ and LAZ were both lower in infants delivered by caesarean section (Figure 1b). There was a consistent pattern in the *z*-scores with respect to mother's education, with infants of mothers who completed secondary school having higher WAZ and LAZ both overall (Figure 2a) and when stratified by infant feeding practice (Figure 2b,c). A similar overall pattern was observed for in-utero exposure to ART: infants with a shorter exposure had consistently higher WAZ and LAZ (Figure 3a), and in stratified analysis, this pattern was observed for infants who were breastfed following WHO recommendations (Figure 3b,c).

From an unadjusted regression model (Table 2, Columns 1 and 2), infants of more highly educated mothers had LAZ scores that were one third of a standard deviation higher than infants of the less

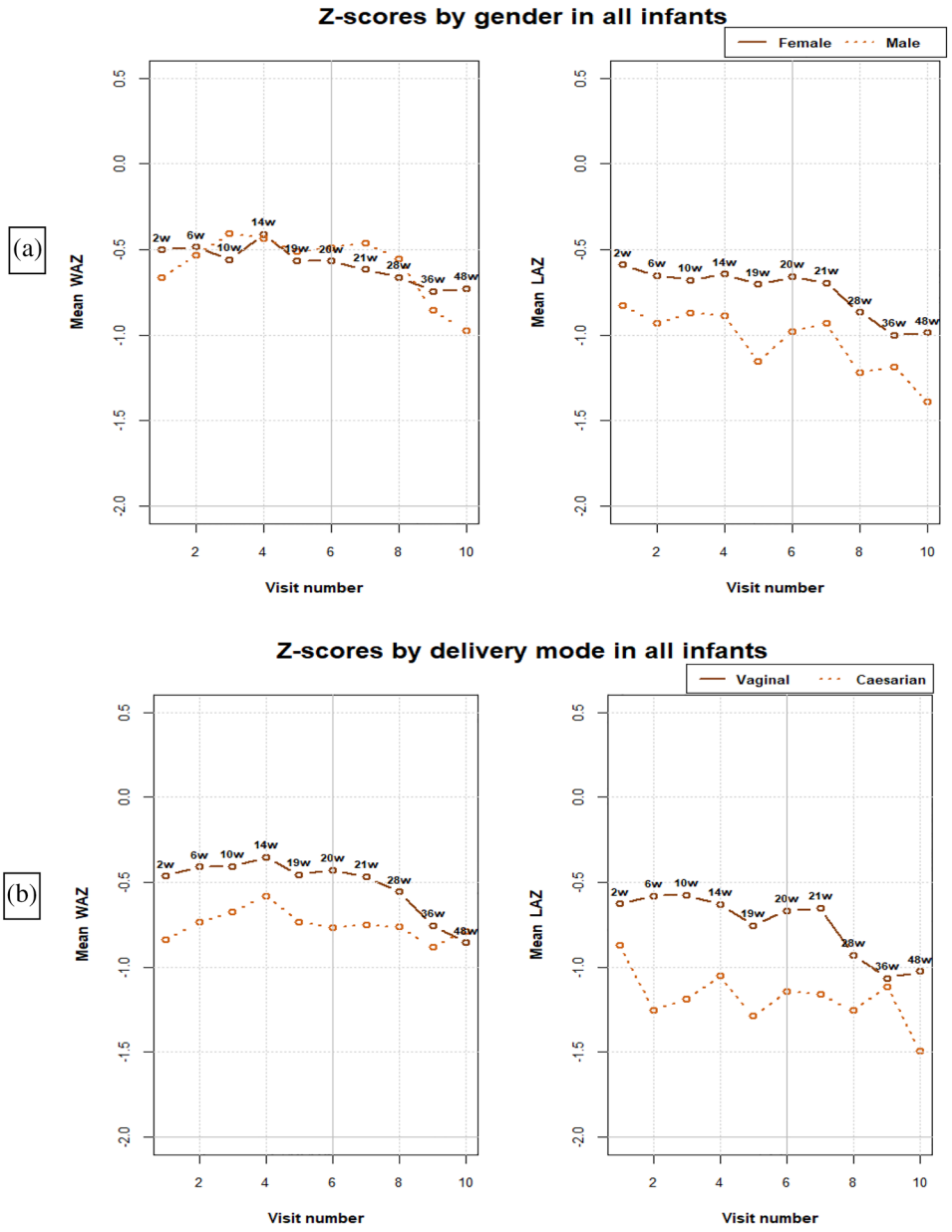

FIGURE 1 Infant growth outcomes stratified by gender (a) and by mode of delivery (b). LAZ, length-for-age *z*-score; WAZ, weight-for-age *z*-score

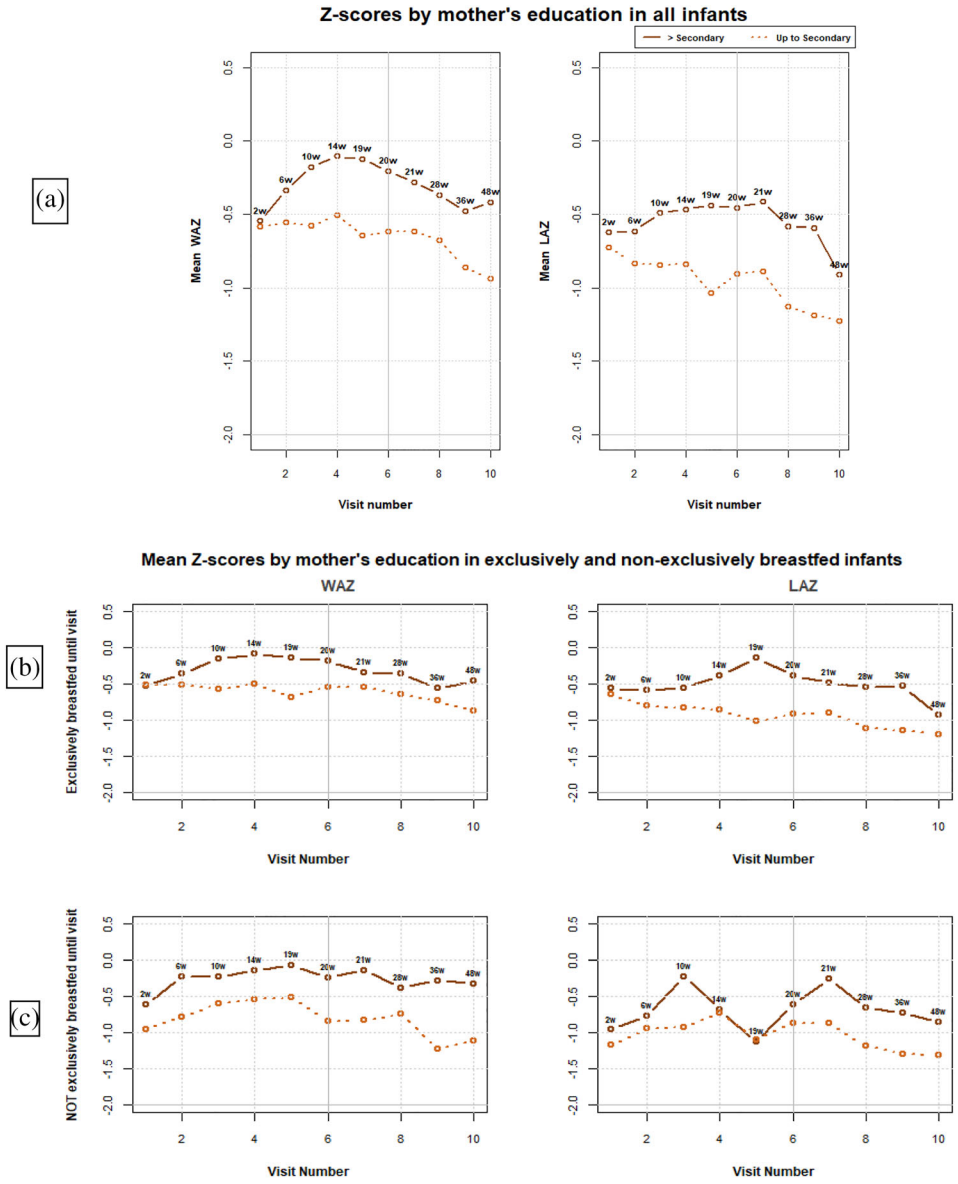

FIGURE 2 The impact of mother's educational level on growth, overall (a) and stratified by feeding mode (b and c). LAZ, length-for-age *z*-score; WAZ, weight-for-age *z*-score

educated mothers (coefficient: 0.35, $p = 0.02$), and there was a trend for a similar magnitude of difference in the WAZ scores (coefficient 0.33, $p = 0.09$). After adjustment for other risk factors (Table 2, Columns 3 and 4), both WAZ and LAZ were significantly higher in the infants of the more educated mothers (WAZ: 0.41, $p = 0.038$; LAZ: 0.48, $p < 0.001$). Longer in-utero exposure to ART and caesarean delivery were independently associated with lower LAZ scores, with similar magnitude of these effects (ART adjusted coefficient: −0.57, $p < 0.001$; caesarean coefficient: −0.32, $p = 0.043$). Lower WAZ (reduction of more than a third of a standard deviation) was also independently associated with longer in-utero exposure ($p = 0.015$). A sensitivity analysis excluding women with inconsistent information regarding their use of ARV medication before/at screening yielded similar results except for reduced significance of the effect of mode of delivery on LAZ (adjusted coefficient: −0.28, $p = 0.078$).

Investigation of interactions indicated that higher educational level conferred an advantage on LAZ, but not WAZ, of infants not exclusively breastfed ($p = 0.015$), with no effect seen among exclusively breastfed infants (Figures S3 and S4a). For WAZ, there was evidence of an interaction between mother's education level and breastfeeding in the first 10 weeks ($p = 0.016$; Figure S4b,c).

Regarding the investigational vaccine, there were no significant differences between the *z*-scores for vaccinated and unvaccinated infants (data not shown).

4 | DISCUSSION

In this study of HEU infants participating in an HIV vaccine trial, we found that 30% were stunted by 1 year of age. This high prevalence of stunting, despite enrolment of a healthy group of HEU infants, underscores the importance of growth monitoring and optimization among HEU children. Infants in the vaccine arm had no evidence of growth compromise compared with the control arm, adding to safety

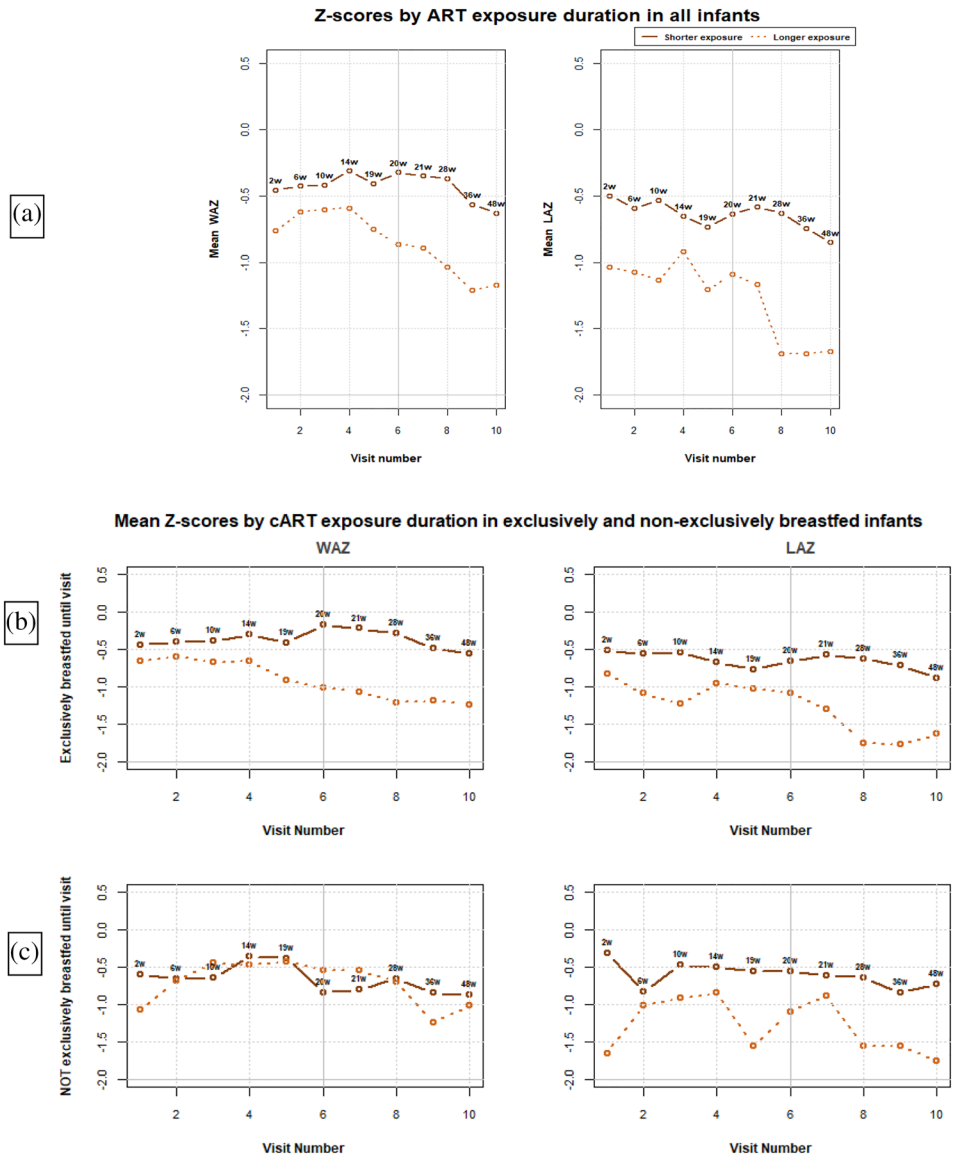

FIGURE 3 The impact of duration of cART exposure on growth, overall (a) and stratified by feeding mode (b and c). ART, antiretroviral therapy; LAZ, length-for-age *z*-score; WAZ, weight-for-age *z*-score

TABLE 2 Coefficients and *p* values from mixed models with piecewise linear splines (two knots at 10 and 21 weeks), random intercept and fixed effects for risk factors

Risk factors	WAZ	LAZ	WAZ adj	LAZ adj
Male	−0.00 (0.995)	−0.26 (0.112)	0.07 (0.686)	−0.15 (0.330)
Exclusive breastfeeding	−0.08 (0.761)	−0.13 (0.484)	−0.11 (0.691)	−0.19 (0.278)
Education[a]	0.33 (0.093)	0.35 (0.022)	0.41 (0.038)	0.48 (0.000)
Caesarean[b]	−0.19 (0.314)	−0.38 (0.022)	−0.17 (0.393)	−0.32 (0.043)
Longer in-utero exposure to ART	−0.37 (0.036)	−0.57 (0.000)	−0.41 (0.015)	−0.57 (0.000)

Abbreviations: ART, antiretroviral therapy; LAZ, length-for-age *z*-score; WAZ, weight-for-age *z*-score; WLZ, weight-for-length *z*-score.
[a]Higher than secondary school.
[b]Either elective or emergency caesarean.

data regarding the vaccine. We found that both WAZ and LAZ were significantly lower among infants with lower maternal education and those with in-utero ART exposure from a median gestational age of 28 weeks. In addition, LAZ was lower among infants born by caesarean section.

There was no strong statistical evidence of an effect of sex on growth, although different growth patterns were seen for WAZ and LAZ, with male LAZ curves being on average below those of females at all ages. These graphical differences, despite the explicit sex adjustment of the *z*-scores, may correspond to an actual larger growth

compromise in boys. This is consistent with results from the Kenya Demographic and Health Survey (Kenya National Central Bureau of Statistics [CBS], 2004), in which there was a higher prevalence of stunting among male children. Maternal CD4 count was not associated with infant growth, likely because the women in this study had relatively high CD4 counts (>350 cells per cubic millimetres) and because ART may decrease the adverse effects of maternal HIV infection on infant growth.

The observed negative effect of caesarean delivery, most notably on LAZ, has not been reported previously for HEU infants. A study of US children observed higher WLZ during the first year of life among children delivered by caesarean section than those delivered vaginally (Mueller, Zhang, Hoyo, Østbye, & Benjamin-Neelon, 2019), but this study was conducted in a cohort with a high prevalence of obesity and not comparable with our study population. Caesarean section has been shown to impact on the gut microbiota in newborns and to be associated with neonatal respiratory morbidity in a large cohort of HEU newborns in Latin America and the Caribbean (Kreitchmann et al., 2011), which could be mediators of the effect on growth.

As previously reported (McDonald et al., 2012; McGrath et al., 2012; Muhangi et al., 2013; Webb, Manji, Fawzi, & Villamor, 2008), maternal education was an independent predictor of both WAZ and LAZ in our study. In addition, we found that the effect on LAZ was modified by breastfeeding practice, with infants of mothers with low education level doing significantly worse if not exclusively breastfed. A modification of the effect of education on WAZ was also seen in the first 10 weeks, underscoring the importance of exclusive breastfeeding on early HEU infant growth. Breastfeeding was also found to limit precipitous WAZ decrease among HEU Zambian infants aged between 4.5 and 15 months (Arpadi et al., 2009). Despite these important contributions of breastfeeding, we did not find any significant overall effect, although a comparison of the average *z*-scores in exclusively breastfed and formula-fed infants at some critical ages (2 weeks, 5–6 months, 9 months and 1 year) suggested an advantage from exclusive breastfeeding: weight-for-age was higher at all four time points, length-for-age was higher except at Months 5–6 and weight-for-length was higher except at Week 2. None of these comparisons reached statistical significance, which may be due to limited statistical power, as the vast majority of study infants (80%) were breastfed until 6 months of age, in line with then current WHO recommendations (WHO, 2010).

In our study, infants with in-utero exposure to ART from a median age of 28 weeks gestation had lower WAZ and LAZ compared with infants exposed for a shorter duration. Several studies suggest that ART exposure may influence the growth of HEU infants. A European collaborative study in 2005 (Hankin, Thorne, & Newell, 2005) found a marginal effect of ART exposure, but a majority of the study infants were white and thus not representative of our study population. However, a US study, where the majority of infants were African-American (Siberry et al., 2012), reported poorer growth at 1 year in infants exposed to combination treatment containing TDF (tenofovir disoproxil fumarate). Duration of exposure in utero to maternal treatment was also investigated in the pre-ART era in Thailand (Briand et al., 2006), where infants exposed to ZDV in utero for more than 7.5 weeks had lower birthweight *z*-scores than infants exposed for a shorter duration. Perhaps the most comparable investigation to ours is the work in Botswana (Powis et al., 2011), which used longitudinal analysis to assess the growth of breastfed HEU infants during the first 6 months of life. These authors demonstrated that breastfed infants exposed to ART in utero had significantly lower weight (during the first 3 months of life) and length, than the breastfed, ZDV-exposed infants. The lower LAZ among ART-exposed infants persisted until 6 months of age. In an extended analysis of the same cohorts (Powis et al., 2016), WAZ and LAZ at 24 months of age were lower in ART-exposed infants compared to ZDV-exposed infants. Although our study does not directly compare infants of women on monotherapy versus those of women on ART, 20% of the group with shorter exposure to ART was on monotherapy before switching to combined ART after their screening visit. A Canadian study (Kakkar et al., 2016) also reported lower weight and smaller head circumference at birth in ART-exposed infants compared with ZDV-exposed infants.

The choice of infant prophylaxis regimen to prevent HIV transmission through breast milk may also be relevant to growth. The secondary analysis of the ANRS 12174 study (Blanche et al., 2019) conducted in African infants from Burkino Faso, South Africa, Uganda and Zambia, reported that exposure to lopinavir–ritonavir was associated with poorer growth outcomes than exposure to lamivudine up to the cessation of breastfeeding. However, in our study, the same prophylaxis regimen was provided to all infants. Interestingly, a study of the effect of treatment of HIV-infected infants (Barlow-Mosha et al., 2016) with lopinavir–ritonavir (compared with nevirapine), despite higher CD4 count and higher rates of virologic failure, reported marginally better WAZ for nevirapine, but no difference in LAZ.

A limitation of our study is the small sample size and the absence of a control group of unexposed, uninfected infants. However, the randomized trial resulted in high-quality data, with close follow-up on each infant and an unbiased assessment of the effect of the candidate vaccine. The inclusion criteria for the trial may have hampered our ability to detect the effect of mother's disease status, as mothers were excluded if their CD4 count was below 350 cells per microlitre. Additionally, an inclusion criterion for the infants was a minimum birthweight of 2,500 g, and infants were excluded from randomization if they had WAZ < −2 SD at 20 weeks of age. Thus, we studied relatively healthy mother–infant pairs, possibly not representative of the general HEU infant population, so that an association between maternal immune status and HEU-infant growth could have been missed. Another limitation of our study is the lack of precise knowledge of the duration of mother's ART prior to the screening visit, which would provide a precise measure of the exposure time of the fetus.

In conclusion, this work highlights the need for studies of the growth patterns of HEU infants and the identification of risk factors for depressed growth in this population. We found no evidence of growth being associated with the MVA.HIVA vaccine and demonstrated the importance of exclusive breastfeeding in mitigating the adverse effects

of lower education. We highlighted the potential need to expand research on the effect of caesarean section on HEU infants in low resource settings. With wide implementation of PMTCT programmes and consequent infant ART exposure, continued evaluation and optimization of growth outcomes among HEU infants will be important.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

CONTRIBUTIONS

This study was conceived by MR with KS and AN; MR, IN and WJ made critical contributions to the acquisition of data; data analysis was carried out by AN and KS; the manuscript was drafted by KS, MR and AN, revised for interpretation and critical content by IN, GJ and TH, and following revisions, approved by all authors for submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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