Growth Trajectories Over the First Year of Life Among Early-Treated Infants with Human Immunodeficiency Virus and Infants Who are Human Immunodeficiency Virus-Exposed Uninfected

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Objective To investigate the role of early antiretroviral therapy (ART) on growth trajectories of infants with human immunodeficiency virus (IHIV) in the first year of life.

Study design As part of a clinical trial of early ART in Johannesburg, South Africa (2015-2018), 116 IHIV diagnosed within 48 hours of birth were started on ART as soon as possible, and 80 uninfected infants born to mothers living with HIV (IHEU) were enrolled. Both groups were followed prospectively from birth through 48 weeks and growth parameters collected. The groups were compared and risk factors for poor growth investigated, in the full cohort and among IHIV separately.

Results IHIV had lower mean weight-for-age Z-scores (WAZ) than IHEU at 4 and 8 weeks (−1.17 [SE:0.14] vs −0.72 [0.14], P = .035 and −1.23 [0.15] vs −0.67 [0.14], P = .012). Although there was some closing of the gap over time, means remained lower in IHIV through 48 weeks. In length-for-age Z-scores (LAZ), differences widened over time and IHIV had lower Z-scores by 48 weeks (−1.41 [0.15] vs −0.80 [0.18], P = .011). Deficits in WAZ and LAZ in IHIV vs IHEU were most marked among girls. IHIV with pre-ART viral load ≥1000 copies/ml had significantly lower weight-for-length and mid-upper arm circumference Z-scores across all time points through 48 weeks.

Conclusions IHIV on early ART had deficits in WAZ over the first 8 weeks of life and lower LAZ at 48 weeks than IHEU. Among IHIV, higher pre-ART viral load was associated with worse anthropometric indicators through 48 weeks. *(J Pediatr 2024;270:114018)*.

Advances in treatment have resulted in dramatically improved outcomes for people living with human immunodeficiency virus (HIV), including children. This includes the markedly decreased vertical transmission rates and improved birth outcomes for infants born to women living with HIV following introduction of universal maternal combination antiretroviral therapy (ART) during pregnancy continued throughout breastfeeding and beyond.[1-3] Furthermore, it is now well-established that infants living with HIV (IHIV) should initiate ART as early in life as possible to suppress viral replication, reduce morbidity and mortality, and improve growth outcomes.[4,5]

Growth trajectories are an important marker of child health. Linear growth velocity, in particular, is an important predictor of survival and cognitive and motor development.[6] In IHIV, poor growth is associated with increased microbial translocation, immune activation and exhaustion, and with an impaired response to ART.[7] Moreover, deficiencies in growth may indicate a failure of ART.[8] Integral care for mothers and families is also essential to growth trajectory associated to HIV exposure. Recent research has pointed to the syndemic interaction between maternal HIV, hazardous alcohol use, and household food insecurity related to underweight in children exposed to HIV but uninfected.[9]

More than 90% of children living with HIV reside in sub-Saharan Africa, where under 5 mortality remains high.[10] Those who reach adolescence have delayed sexual development compared to youth HIV exposed uninfected.[11-13] Poor growth and pubertal delay in adolescents with HIV, may be associated with

IHIV	Infants with HIV
HCAZ	Head circumference for age
IHEU	Infants HIV-exposed uninfected
ART	Antiretroviral therapy
MUAC	Mid-upper arm circumference
MUACZ	Mid-upper arm circumference for age Z-score
HIV	Human immunodeficiency virus
POC	Point-of-care
VL	Viral load
WAZ	Weight-for-age Z-scores
GEE	Generalized estimating equations

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long-term negative consequences, such as reduced adult height and lower bone mineral density, poor psychosocial functioning, and educational attainment, as well as increased susceptibility to metabolic and cardiovascular disorders.[14,15] Sexual development delay is associated with age at ART initiation and deficits in growth in the first years of life.[12]

South Africa has the largest population living with HIV and the greatest numbers of children and adolescents affected worldwide.[16] Despite early ART and largely well-controlled disease, growth deficits are still detectable in children with HIV in comparison to World Health Organization (WHO) norms and children who are HIV-uninfected.[17] Very early initiation of ART, ie during the first weeks of life during the neonatal period, has only been possible in more recent years with the expansion of birth testing programs. The impact of ART initiation very early in life on growth is not well described.

The aim of this study was to examine the influence of very early ART on the growth patterns of a cohort of South African IHIV during their first year of life, compared to infants exposed to HIV but uninfected (IHEU). We also investigate the role of maternal and infant factors on growth trajectories in IHIV and IHEU combined and in IHIV separately. Optimizing postnatal growth can significantly impact health outcomes in adulthood. This will contribute to alleviating the challenges faced by families affected by HIV already dealing with stigma and difficult social and economic conditions.

Methods

Study Sample

This is a longitudinal analysis of data collected from a cohort of 116 IHIV enrolled in a clinical trial of early ART (clinicaltrials.gov: NCT02431975)[18] and a cohort of 80 IHEU followed between August 2015 and August 2018. The study was conducted at Rahima Moosa Mother and Child Hospital, a large, tertiary hospital, centrally-located in Johannesburg, South Africa. The institutional review boards of the University of the Witwatersrand and Columbia University approved the study. Written informed consent was obtained from all mothers.

Study Procedures

All infants included in the study were identified in the hospital's postnatal wards. As part of routine services, all infants born to women with HIV had heel stick blood samples collected <48 hours of birth that were sent to the National Health Laboratory Service for nucleic acid amplification testing (COBAS TaqMan HIV-1 Qualitative Test Version 2.0, Roche Molecular Systems, Inc., Branchburg, NJ) with approximately 48 hours turn-around time. Coverage of the routine testing program was >93%.[19] In addition, when staff capacity allowed, postpartum women living with HIV were offered testing with an on-site, point-of-care (POC) test (Xpert HIV-1 Qualitative assay, Cepheid) with results returned in approximately 2 hours. Coverage of POC testing was 50%.[19] Positive POC tests were repeated on residual sample and neonates with 2 positive POC tests were eligible for immediate ART initiation prior to discharge. If missed by the POC testing program, but with positive results returned from the routine testing program, patients were recalled to the site and started on ART as soon as possible. Repeat blood samples were drawn prior to ART start in all infants. Infants whose initial positive results were not confirmed were excluded.

A comparison cohort of 80 IHEU was recruited over the same period. This cohort included 69 infants who tested negative on the birth POC test and 11 infants who had positive or indeterminate results on the routine laboratory-based test or inconsistent POC results on samples collected within 48 hours of birth. Infants were followed with multiple repeat testing over the first year of life and 1 infant who had tested negative on the POC test at birth who had a later positive result was excluded. The remaining infants had consistently negative results. No children with unresolved or equivocal results after repeat testing were retained in this analysis.[20,21]

The starting regimen for IHIV consisted of nevirapine, lamivudine and zidovudine if < 42 weeks postmenstrual age. Nevirapine was changed to lopinavir-ritonavir no sooner than 42 weeks postmenstrual age accounting for patient readiness. At 3 months abacavir was substituted for zidovudine. Alternate regimens were used as necessitated by comorbid conditions. Cotrimoxazole was started and stopped in both groups and continued as per South African guidelines in place at the time.[22] Postnatal prophylaxis for IHEU consisted of daily nevirapine for 6 weeks. IHEU considered high risk had twice-daily zidovudine added.

Measurements

Maternal viral load (VL) was measured at enrollment (COBAS AmpliPrep/COBAS TaqMan HIV-1 test, v2.0, Roche Molecular Systems, Inc) as well as CD4+ T-cell counts (TruCount Method, BD Biosciences, Heidelberg, Germany). Data on maternal VLs and CD4 counts measured during and before pregnancy were abstracted from antenatal records along with maternal ART history. Other maternal factors including alcohol use, smoking, parity, education, and marital status were recorded on study forms following interview with the mother. Data on infant birth weight, gestational age, and mode of delivery were abstracted from delivery records. Pre-ART IHIV VL and CD4+ T-cell counts and percentages were measured.

Follow-up visits occurred at 1, 2, 4, 8, 12, 16, 20, 24, 36, and 48 weeks of age for IHIV and at 4, 8, 12, 24, 36, and 48 weeks of age for IHEU. Weight, length, and head circumference (HC) were measured by trained study staff using calibrated equipment according to a standard protocol at each of these visits. Mid-upper arm circumference (MUAC) was measured at 12, 24, 36, and 48 weeks. Weight was obtained using a digital scale and documented to 2 decimal places, recumbent length was measured using a rigid infantometer and recorded to 1 decimal place, head-circumference and MUAC were

measured using a flexible anthropometric tape-measure documented to 1 decimal place.

Low birth weight (LBW) was defined as birth weight <2500 grams (g).[23] Preterm birth was defined as gestational age <37 weeks and was determined by clinical staff trained in the Ballard score and gestational age estimated from the Ballard, as well as from any available ultrasounds, examinations or last menstrual period recorded in antenatal records. WHO child growth standards were used to generate Z-scores for each of 5 standardized measures: weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ), MUAC for age Z-score (MUACZ), and head circumference for age (HCAZ). LAZ <−2 were classified as stunting, and WAZ ≥1 as overweight.[24] Breastfeeding data were recorded on study forms and updated at each follow-up visit.

Statistical Analysis

Maternal and infant characteristics were compared by child's HIV infection status using χ^2 or Fisher's Exact tests, Wilcoxon rank-sum tests, and t-tests. To examine the association between HIV status and other factors on WAZ, LAZ, WLZ, HCAZ and MUACZ at each time point independent *t* tests were performed. Differences between the groups over all the time points were studied using generalized estimating equations (GEE) of repeated measures. Multivariable GEE models were built by adjusting for covariates significant in univariable analysis. Interaction terms were used to evaluate effect modification by sex. Separate GEE models were fit to investigate factors associated with growth in the entire cohort and in IHIV separately. The *P*-value threshold for statistical significance was <0.05. Analyses were conducted using SAS software version 9.4.

Results

General Sample Characteristics

We recruited 116 IHIV diagnosed <48 hours of birth who started ART as soon as possible, and 80 IHEU controls (**Table I**). Mothers of IHIV had higher VL, lower CD4 counts and less ART use than mothers of IHEU and were younger and less likely to be married. There were no significant differences in birthweight, percentages with LBW, or length or HC at birth by group. Preterm birth tended to be more common among IHIV (15% vs 6%, $P = .067$). Cesarean delivery was most frequent in IHIV (28% vs 4%, $P < .0001$). Breastfeeding uptake was similar across the groups. Fifty percent of IHIV started ART in the first 48 hours of life, 75% started within a week and 94% within 28 days (range: 8.1 hours-148 days). Among IHIV the median pre-ART VL was 29 202 copies/ml (IQR: 2380-240,810) and 21% had a CD4% <30% (**Table I**).

Growth Trajectories Over 48 Weeks of Life

Anthropometric indicators over the first 48 weeks of life for IHIV and IHEU are shown in **Figure 1**. WAZ was consistently lower in IHIV than in IHEU through 48 weeks. The differences were statistically significant at 4 and 8 weeks (−1.17 vs −0.72, $P = .035$ and −1.23 vs −0.67, $P = .012$). There was some catch up in WAZ after 8 weeks in IHIV and from 12 weeks in IHEU, but by 48 weeks, the mean Z-score in IHIV was −0.8 and −0.4 in IHEU (**Figure 1**A). Eight percent of IHIV (9/116) and 12% (10/80) of IHEU were overweight at 48 weeks ($P = .4980$). This WAZ pattern by HIV status was maintained in analyses restricted to infants born at term with birth weight ≥2500g (**Figure 1**, online; available at www.jpeds.com).

Mean LAZ was well below zero but was similar in the 2 groups at the first measurement at 4 weeks. At 8 weeks, mean LAZ was lower in IHIV than in IHEU ($P = .042$). IHEU improved their Z-score with age, although the mean Z-score in this group did not reach norms for children at 48 weeks despite this increasing trend, with a mean of −0.8 at 48 weeks. By 48 weeks, LAZ was significantly lower in IHIV than in IHEU (−1.41 vs −0.80, $P = .011$) (**Figure 1**B). Thirty percent of IHIV and 12% of IHEU were stunted at 48 weeks ($P = .012$). Infants born at term with birth weight ≥2500g (IHIV = 90 and IHEU = 68) had the same pattern of LAZ over time with significant differences at 48 weeks between the groups (**Figure 1**, online; available at www.jpeds.com).

Mean WLZ was lower among IHIV at 4 weeks but thereafter was similar to IHEU. There were no significant differences between the groups in HCAZ measurements (**Figure 1**C, D). There were also no differences between IHIV and IHEU in MUACZ-scores measured at 12, 24, 36, and 48 weeks (results not shown).

Factors Associated with Growth in IHIV and IHEU

Sex Differences. Mean WAZ was lower in male vs female infants over the 48-week period although this did not reach statistical significance after adjustment for prematurity ($\beta = -0.2114$, SE = 0.16 $P = .186$) (**Figure 2**A). Males also had lower LAZ than females, a difference which was not significant overall after adjustment for prematurity ($\beta = -0.2783$, SE = 0.16 $P = .081$) but was significant at 12 and 24 weeks (**Figure 2**B).

When investigating the effect of HIV status within males and females separately, differences between IHIV and IHEU were most marked in girls. WAZ was significantly lower in female IHIV over the 48 weeks overall and at 4, 8, and 12 weeks (**Figure 2**C). LAZ was also lower in female IHIV vs IHEU overall and significantly lower at 8, 12, 24, and 36 weeks (**Figure 2**D). Trajectories over time of WAZ and LAZ between IHIV and IHEU in males were largely similar (**Figure 2**E, F). The interaction term between sex and HIV status was not significant ($P = .168$).

Other Factors Associated with Growth. Preterm birth, LBW, cesarean delivery, lower maternal CD4 counts, being a single mother, and smoking or drinking during pregnancy were associated with WAZ across 48 weeks in univariable analysis (**Figure 2**A, online; available at www.jpeds.com). Factors associated with LAZ were similar, with the addition of significantly lower LAZ for male infants. In multivariable

Table I. Maternal characteristics and birth parameters of 116 infants with HIV (IHIV) and 80 infants who are HIV-exposed uninfected (IHEU) born at Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa, Aug 2015-Aug 2018

	IHIV (=116)	IHEU (=80)	All	*P*-value
Maternal characteristics				
Mother age (years), mean (SD)	27.93 (5.8)	30.20 (5.45)	30.16 (5.48)	.006
Maternal ART n (%)				
ART before pregnancy and continued	16 (14)	27 (34)	43 (22)	<.0001
ART during pregnancy, ≥ 12 weeks	34 (29)	41 (51)	75 (38)	
ART during pregnancy, <12 weeks	40 (34)	8 (10)	48 (25)	
ART during pregnancy, unknown	1 (1)	1 (1)	2 (1)	
No ART up until delivery	25 (22)	3 (4)	28 (14)	
Maternal CD4 count closest to birth (cells/mm^3), Median (IQR)	346.5 (224.5-570)	524.5 (358- 718.5)	437.5 (266.0- 648.5)	<.0001
Maternal CD4 count closest to birth (cells/mm^3), n (%)				<.0001
<350	59 (51)	17 (21)	76 (39)	
≥350	57 (49)	63 (79)	120 (61)	
Maternal HIV RNA closest to birth (copies/ml) n (%)				<.0001
<1000	29 (25)	66 (83)	95 (48)	
≥1000	87 (75)	14 (17)	101 (52)	
Maternal $\log_{10}$ HIV RNA closest to birth (copies/ml), Median (IQR)	4.55 (2.94-5.02)	1.32 (0-2.04)	3.16 (1.32- 4.83)	<.0001
Parity (number), mean (SD)	2.43 (1.14)	2.49 (0.98)	2.54 (1.08)	.477
Median (IQR)	2 (2-3)	2.5 (2-3)	2 (2-3)	
Smoked during pregnancy n (%)				
No	111 (96)	76 (95)	187 (95)	.821
Yes	5 (4)	4 (5)	9 (5)	
Alcohol during pregnancy n (%)				
No	111 (96)	74 (93)	185 (94)	.340
Yes	5 (4)	6 (7)	11 (6)	
School grade n (%)				
< 12 th grade	73 (63)	45 (56)	118 (60)	.274
≥ 12 th grade	41 (35)	35 (44)	76 (40)	
Marital status n (%)				
Single	91 (78)	46 (58)	137 (70)	.0017
Married	25 (22)	34 (42)	59 (30)	
Infant characteristics				
On site point of care test tested n (%)				
Yes	64 (55)	74 (93)	138 (70)	<.0001
No	52 (45)	6 (7)	58 (30)	
Child Sex n (%)				
Male	54 (47)	41 (51)	95 (48)	.518
Female	62 (53)	39 (49)	101 (52)	
Mode of delivery, n (%)				
NVD	83 (72)	77 (96)	160 (82)	<.0001
CS	33 (28)	3 (4)	36 (18)	
Gestational age (weeks), n (%)				.067
<37 weeks (pre-term)	17 (15)	5 (6)	22 (11)	
≥37 weeks (term)	99 (85)	75 (94)	174 (89)	
Birth Weight (g), n (%)				.808
<2500	23 (20)	17 (21)	40 (20)	
≥2500	93 (80)	63 (79)	156 (80)	
Birth weight (g), mean (SD)	2835 (565.91)	2946.63 (499.75)	2880.74 (541.34)	.158
Birth length (cm), mean (SD)	48.51 (3.81)	48.64 (3.38)	48.56 (3.64)	.808
Birth head circumference (cm), mean (SD)	33.93 (2.14)	33.74 (1.70)	33.85 (1.97)	.511
Ever Breastfed n (%)				
Yes	91 (78)	58 (73)	149 (76.)	.338
No	25 (22)	22 (27)	47 (24)	
Age at ART start, n (%)				
0 to ≤ 48 hours	58 (50)			
>48 hours to 7 days	29 (25)			
8-14 days	14 (12)			
≥ 15 days	15 (13)			
Min-max (days)	0-148			
Infant pre-ART VL (copies/ml) median (IQR)	29 202 (2380-240 810)			
Infant HIV RNA pre-ART (copies/ml), n (%)				
<1000	31 (27)			
≥1000	85 (73)			
Infant CD4 count, pre-ART (cell/mm3), n (%)				
<1500	26 (28)			
≥1500	66 (72)			

(*continued*)

Table I. Continued

	IHIV (=116)	IHEU (=80)	All	*P*-value
Infant CD4 percent (%), pre-ART, n (%)				
<30	19 (21)			
≥30	73 (79)			
Infant CD4 count, pre-ART (cell/mm3), Median (IQR)	1895 (1474-2604)			
Infant CD4 percent (%), median (IQR)	40.7 (31.9-50.8)			

Abbreviations: n, infant number; SD, standard deviation; IQR, interquartile range; NVD, normal vaginal delivery; CS, cesarean section.

analysis after adjusting for HIV status and sex, preterm birth and LBW remained associated with WAZ; for LAZ, in addition to these parameters, being male and maternal smoking were also significantly associated (**Figure 2**B, online; available at www.jpeds.com). Neither WAZ nor LAZ over 48 weeks were associated with ever vs never breastfeeding. Further analysis by breastfeeding duration also did not find associations.

A separate multivariable analysis focused on LAZ at 48 weeks was conducted. IHIV had significantly lower LAZ at 48 weeks than IHEU (β = −0.5607, SE = 0.1893 P = .0031) after adjusting for sex, preterm birth, LBW, maternal CD4 count, and maternal alcohol use and smoking during pregnancy.

Factors Associated with Growth in IHIV. Among IHIV, those who were preterm or LBW had lower WAZ and LAZ over 48 weeks. We also investigated age at ART start, and pre-ART VL, CD4 count, and CD4 percent. IHIV who started ART >48 hours had lower WAZ and LAZ at 4 and 8 weeks but the curves converged and were close to identical at later ages (**Figure 3**, online; available at www.jpeds.com). When we repeated this analysis in term infants with normal birth weight, WAZ an LAZ were similar between those who started ART ≤48 hours and started >48 hours in all time point measures. Lower pre–ART CD4 counts and percentages were also associated with lower WAZ and LAZ at 4 weeks, thereafter the trajectories slowly converged and were similar by 48 weeks (**Figure 3**, online; available at www.jpeds.com). When we repeated this analysis in term infants with normal birth weight, the difference between points of measure in WAZ and LAZ trajectories were not remarkable.

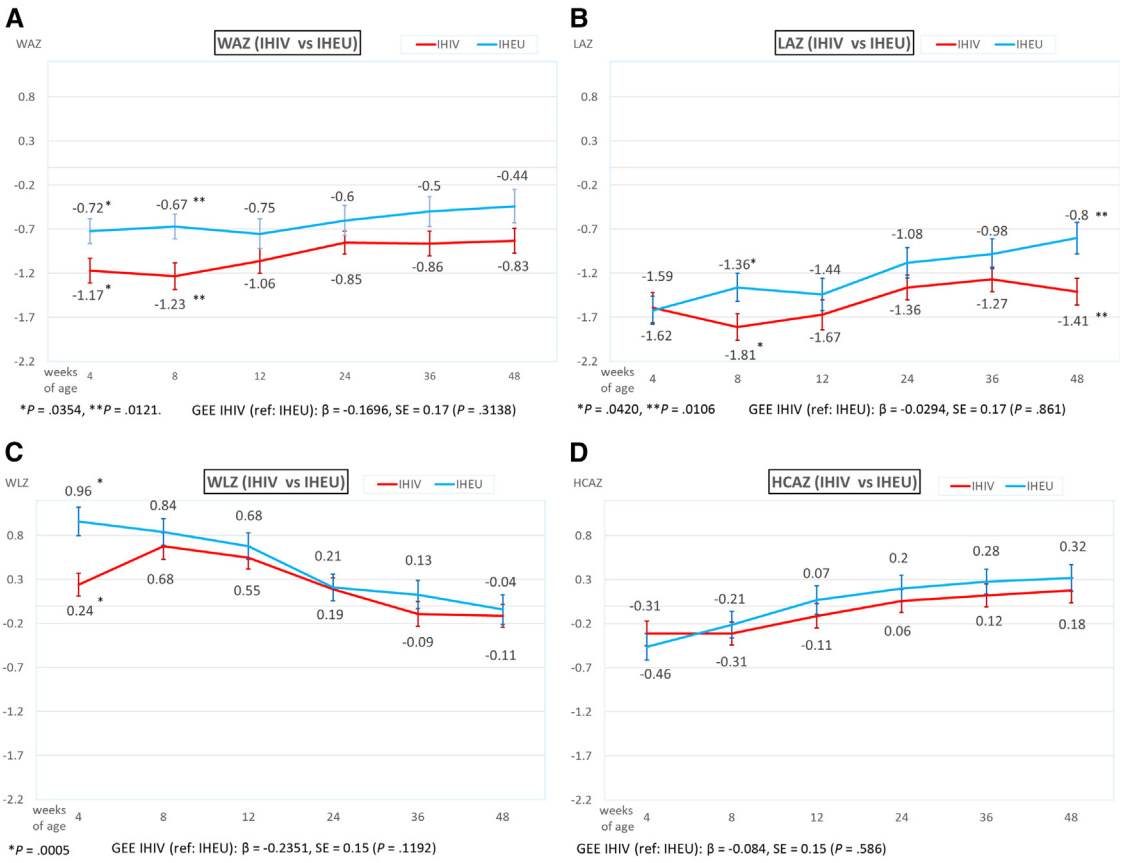
In contrast, pre-ART VL had a distinct association with growth in IHIV (**Figure 3**). IHIV with pre-ART VL ≥ 1000 copies/ml had slightly higher WAZ at the early time points than IHIV with lower VL. From 8 weeks, WAZ was lower in those with higher pre-ART VL and these differences accentuated over time (**Figure 3**A). Pre-ART VL associations with LAZ followed a similar pattern, but associations were less marked (**Figure 3**B). Regarding WLZ, IHIV with pre-ART VL ≥ 1000 copies/ml, despite starting at 4 weeks from the same point, had consistently lower Z-scores across later timepoints than those with lower VL (β = −0.4964, P = .020) (**Figure 3**C). MUACZ curves in IHIV with pre-ART VL ≥ 1000 copies/ml were also significantly lower over all the measured time points (β = −0.8317, P = .0003) than those with lower VL (**Figure 3**D).

In multivariable analysis, adjusted for sex and covariates significant in univariable analysis, the only additional variables significantly associated with the anthropometric indicators in IHIV were LBW, which was associated with all indicators, and low maternal CD4 count which was associated with lower LAZ in IHIV (**Figure 4**, online; available at www.jpeds.com).

Discussion

We investigated growth trajectories in cohorts of infants with intrauterine infection (IHIV) who started ART at very young ages compared with infants HIV-exposed but uninfected (IHEU) in Johannesburg, South Africa. IHIV had lower WAZ at 4 and 8 weeks than IHEU with some catch up by 48 weeks. In contrast, IHIV were similar to IHEU in LAZ at 4 weeks but differences widened over time with significantly lower LAZ at 48 weeks in IHIV compared with IHEU. The mean LAZ in neither group attained WHO standards. These patterns were maintained if analysis was restricted to infants born at term with birth weight ≥2500g. We infer that, despite early ART, there are growth deficits in the first year of life in IHIV that are not explained by birthweight or prematurity. Instead, deficits in WAZ in the early months of life in IHIV despite treatment may explain deficits in LAZ seen at 48 weeks.

A major strength of this work is the repeated growth measures in a sample of children with very early ART start. The extent to which these differences are explained by nonadherence, ART regimen and failure to respond to ART, as well as socioeconomic status or maternal health is difficult to ascertain.[25-27] WAZ was most compromised in the early period with strongest differences on LAZ observed at 48 weeks. These patterns have been observed in other studies with later ages at ART start.[28-30] Despite having escaped HIV infection, IHEU have increased risk of mortality and morbidity as well as impaired early linear growth compared with infants who are not exposed to HIV ie born to women who are HIV negative.[31,32] Both IHIV and IHEU share common prenatal circumstances that affect birth growth parameters.[33] HIV exposure during pregnancy, ART exposure or universal risks, may cluster in families affected by HIV[34] and influence differential trajectories over 48 weeks compared with infants who are HIV-unexposed. In our sample, 30% of IHIV vs 12% IHEU were stunted. However, this percentage of IHIV stunted is similar to the percentage of children stunted in South Africa (27% in 2016).[35] The



E

	WAZ		LAZ		WLZ		HCAZ	
	IHIV (n = 116)	IHEU (n = 80)	IHIV (n = 116)	IHEU(n = 80)	IHIV (n = 116)	IHEU (n = 80)	IHIV (n = 116)	IHEU (n = 80)
Weeks	Available data (n)		Available data(n)		Available data (n)		Available data (n)	
4	96	68	96	68	86	66	93	67
8	100	69	100	69	99	69	98	69
12	95	66	95	66	94	66	92	66
24	100	64	100	64	100	64	96	64
36	95	61	95	61	95	61	93	61
48	85	51	85	51	85	51	85	51

Figure 1. **A,** WAZ **B,** LAZ, **C,** WLZ and **D,** HCAZ at 4, 8, 12, 24, 36, and 48 weeks of age among IHIV and infants who are HIV-exposed uninfected (IHEU). **E,** Number of infants with this measurement at each time point. β, parameter coefficient for HIV status adjusted for preterm birth and SE.

percentage of overweight was relatively high in IHEU and IHIV (12% and 8%) consistent with previously published data with short durations of breastfeeding.[36] Controlling overweight is essential since it is a noncommunicable disease and a risk factor for the development of many other medical conditions.[37]

Our results suggest that sex of the infant could play a role in these patterns. The strongest differences between IHIV and IHEU were observed in girls. Studies on sex differences in the progression of HIV infection have not shown clear differences between VL of females and males before ART.[38,39] Also, results have been inconsistent regarding sex differences in viral suppression in response to ART.[40,41] Females have been shown to have better CD4 T-cell response after ART compared with males, possibly because healthy uninfected female children have higher CD4 T-cell counts.[40] In our study of infants with presumed intrauterine infection there was a slight predominance of females relative to males (62 vs 54), as reported in other studies.[39] It has been theorized that females have increased susceptibility to intrauterine HIV infection, due to exacerbated immune responses that facilitate infection with HIV particularly if the mother is recently infected.[39,42]

Despite the stronger association between HIV status and growth outcomes in girls in our study, males had consistently lower WAZ and LAZ than females over the follow-up period. Under conditions of optimal health and nutrition (WHO references) male infants have slightly but not significant higher WAZ and HAZ in the first 18 months of life.[24] However, male infants in sub-Saharan Africa have a higher prevalence of stunting and wasting.[43] The causes are not clear, but boys are more likely to experience undernutrition. Various factors including biological, social, and combined mechanisms may contribute to these differences.[44] In IHIV, a worse growth trajectory in males in the first 2 years of life with a median

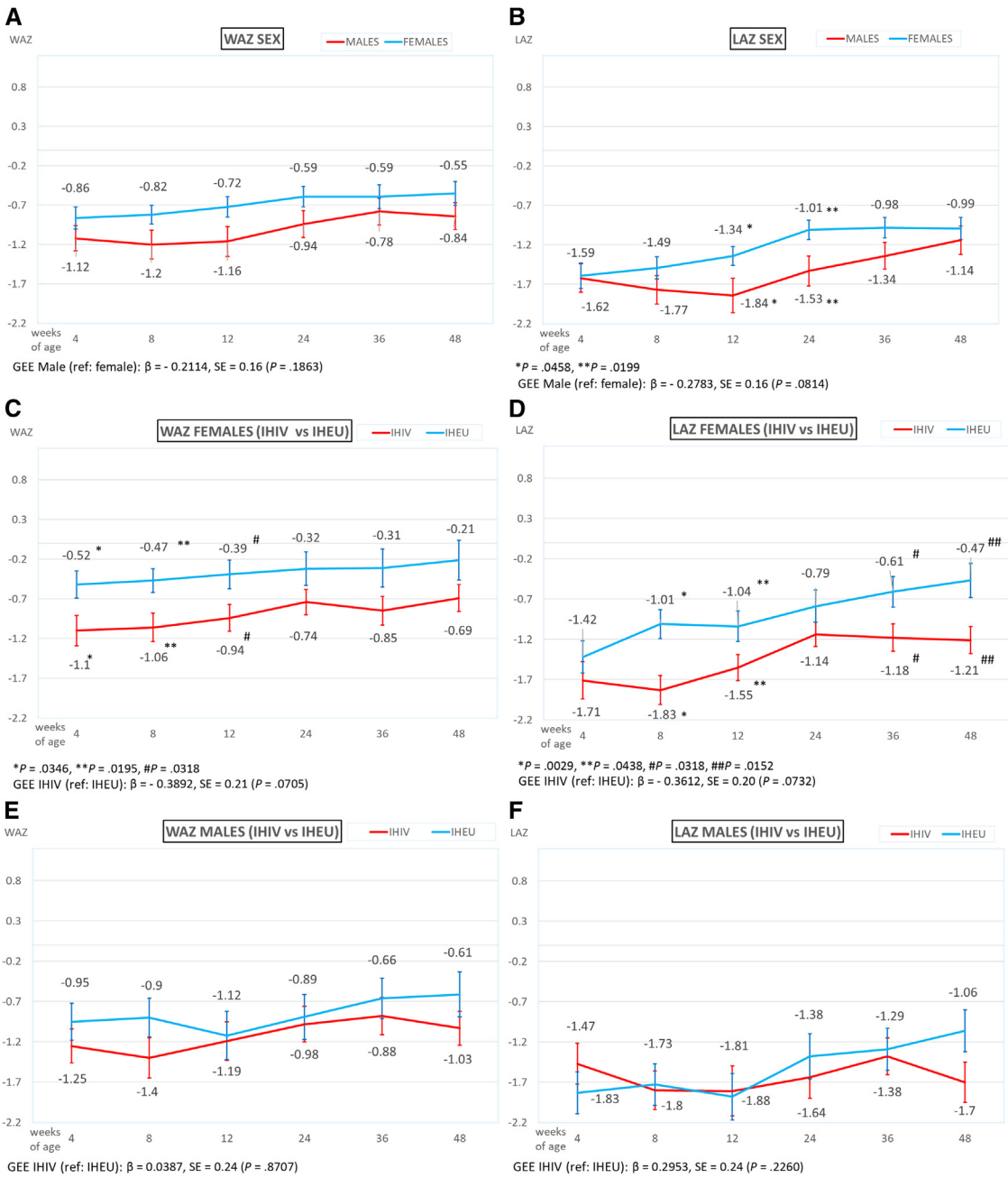


Figure 2. WAZ and LAZ at 4, 8, 12, 24, 36, and 48 weeks of age by sex in the whole cohort **(A, B)**, among females only by HIV status **(C, D)** and among males only by HIV status **(E, F)**. β, parameter coefficient for HIV status adjusted for preterm birth and SE.

ART start of 8 months has been described previously.[40] However, this sex difference was not observed in another study with later ART start.[30] Similarly, in IHEU growth trajectory studies, there are disparate results in relation to sex, with variability between geographical areas.[45-47] Nearly overlapping curves between IHIV and IHEU boys suggest that intrauterine exposure to HIV, not just infection, may have a greater impact on boys and highlight the possibility for more sex differentials. Factors implicated in these differentials are not clear, but early childhood is an excellent time to study sex differences in HIV because social and behavioral disparities are less pronounced than in adulthood.

Several maternal factors, including marital and educational status, alcohol use and smoking during pregnancy, and lower CD4 counts close to delivery were related with lower WAZ and LAZ trajectories in the full cohort. The association of low maternal CD4 counts with deficits in growth was attenuated when adjusted for prematurity and LBW. Twenty-two percent of IHIV mothers and 4% of IHEU mothers in our sample did not receive ART during

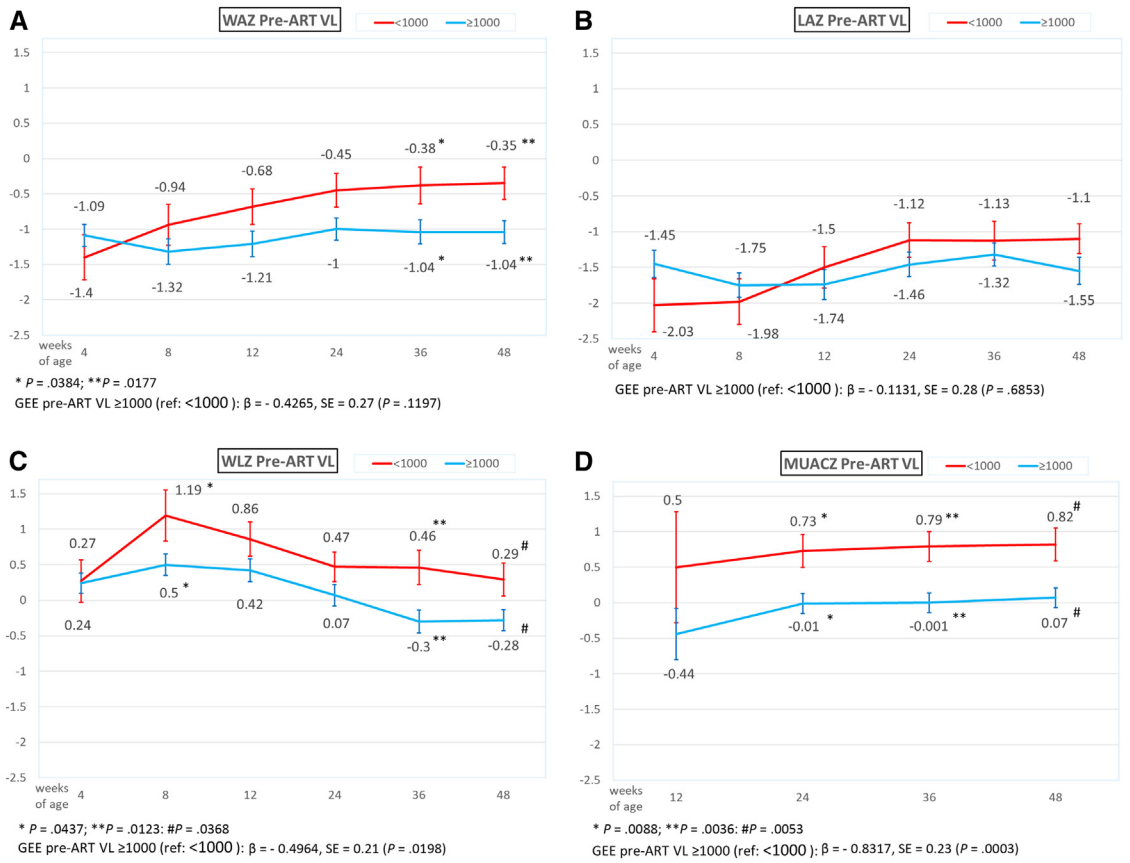


Figure 3. **A,** WAZ **B,** LAZ, **C,** WLZ and **D,** MUACZ at 4, 8, 12, 24, 36, and 48 weeks of age among IHIV by pre-ART viral load (VL). β, parameter coefficient for HIV status adjusted for preterm birth and SE.

pregnancy. Since low maternal CD4 counts, and related markers of disease severity, are associated with increased likelihood of preterm birth and LBW, these findings emphasize the importance of supporting maternal health with earlier diagnosis and ART start in pregnancy to improve birth outcomes[48,49] as well as, possibly, postnatal growth of IHIV and IHEU.

We did not observe consistent benefits of beginning ART especially early (≤48 hours of birth) compared with slightly later. Younger age at ART initiation has been associated with more rapid growth reconstitution[5,30] but these studies include a wider range of ages at treatment initiation, limiting comparison with our study. In our study, more than half of the IHIV started ART under 48 hours of life and almost all within a few weeks of life placing the entire cohort in the category that is conventionally considered early treatment. We interpret the better anthropometric parameters at 4 weeks in those who started ART <48 hours of birth as selection bias. Only infants who underwent POC testing could start ART within 48 hours since the results were available before discharge. The logistics of implementing POC testing meant that infants who required admission were more difficult to reach hence making access to very early ART more difficult for preterm and LBW infants. Age of ART start is strongly associated with viral reservoir size during sustained viral suppression,[50] but the optimal age for ART initiation is still not clear. A focus should remain on the capacity of ART to control morbidity and mortality, and growth is a useful clinical marker in this regard.

Among IHIV, pre-ART VL was not associated with WAZ and LAZ in the early weeks but, over time, higher VL was associated with worse growth. Higher pre-ART VL was also associated with worse WLZ and MUACZ. Lower maternal CD4 count was associated with lower LAZ in IHIV. Infant pre-ART VL and maternal CD4 count were associated with virological response to ART, and infant pre-ART VL associated with maternal VL, in this same cohort.[51] These results add to the evidence base of the importance of supporting maternal health during pregnancy for mothers with HIV.

Our study has limitations. A longer follow-up period is needed to monitor longer-term growth outcomes. A control group of unexposed infants would have been useful for additional comparisons. We used WHO growth standards and not local or specific IHIV growth charts that may be more suitable for infant growth monitoring. Full attendance with every study visit was not achieved which did not allow for growth measurements for all patients at all time points. We did not investigate immune or neuroendocrine mechanisms for growth differences, nor did we consider the different ART treatments of the mothers and infants in our analysis.

Dichotomized variables were used to facilitate analysis and predictive accuracy, with the consequent loss of information. The complexity of viral response to ART precluded adequate investigation of the extent to which these patterns were explained by poor adherence to treatment or correlated with viral control across the first year of life among IHIV.

In conclusion, in our cohort of early treated IHIV, there was significantly lower weight in the first weeks of life with a significant impact on length by 48 weeks of age with values consistently lower than in the IHEU group. Sex differences were also present. Among IHIV, pre-ART VL ≥1000 copies/ml was associated with worse anthropometric indicators over 48 weeks. While research on timing of initiation of ART in children with HIV and viral reservoir size continues, growth in these children should be monitored in parallel to implement its use as a marker of response to ART. ■

CRediT authorship contribution statement

Ana Barrios-Tascon: Data curation, Formal analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Renate Strehlau:** Data curation, Writing – review & editing. **Faeezah Patel:** Data curation, Writing – review & editing. **Megan Burke:** Data curation, Writing – review & editing. **Stephanie Shiau:** Formal analysis, Writing – review & editing. **Yanhan Shen:** Formal analysis, Writing – review & editing. **Stephen M. Arpadi:** Conceptualization, Writing – review & editing. **Elaine J. Abrams:** Investigation, Writing – review & editing. **Caroline T. Tiemessen:** Investigation, Writing – review & editing. **Louise Kuhn:** Conceptualization, Formal analysis, Funding acquisition, Investigation.

Declaration of Competing Interest

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