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Growth differences by school-age and adolescence according to *in utero* and peripartum antiretroviral therapy exposure among Ugandan children

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Abstract

In utero/peripartum antiretroviral (IPA) drug exposure in human immunodeficiency virus (HIV)-exposed children has established benefit for prevention of HIV mother-to-child-transmission but its association with height-for-age by adolescence is unknown. Hence we quantify IPA-associated growth differences at 6 to 18 years old among children with perinatally acquired HIV (CPHIV) infection and children HIV exposed but uninfected (CHEU) relative to children HIV unexposed and uninfected (CHUU). Cohort study. Kampala, Uganda. Two hundred thirty eight community controls and 490 children of women living with HIV born between 2000 and 2011 in a community were enrolled at 6 to 18 years of age and followed every 6 months for 1 year. Height-for-age determined at enrollment, 6 and 12 months after enrollment using the World Health Organization reference. IPA exposure was retrospectively determined from medical records and categorized as: no IPA, single-dose nevirapine with/without zidovudine (sdNVP ± AZT), sdNVP + AZT + lamivudine, or combination antiretroviral therapy (cART). Mean differences (β) with 95% confidence intervals (CIs) in height-for-age over 12 months were evaluated according to IPA exposure for CPHIV and CHEU and relative to CHUU using longitudinal linear mixed effects models adjusted for caregiver factors (sex, age, education, functioning in caregiving role, and lifetime adversity) in Statistical Analysis Software (v.9.4). Regardless of IPA type, CPHIV grew worse than CHUU by school-age/adolescence (β = –0.30, 95% CI: –0.48, –0.11). Relative to CHUU height-for-age was similar for CHEU exposed to sdNVP ± AZT (β = –0.16, 95% CI: –0.46, 0.14) and for CHEU exposed to sdNVP + AZT + lamivudine (β = 0.08, 95% CI: –0.20, 0.35). However, CHEU without any IPA exposure had lower height-for-age (β = –0.27, 95% CI: –0.52, –0.00) whereas CHEU with cART exposure had greater height-for-age (β = 0.41, 95% CI: 0.10, 0.71) in comparison with CHUU by 6 to 18 years old. Our findings suggest that CHEU may achieve height-for-age parity with CHUU by school-age and adolescent years- especially if provided benefit of effective cART in the peripartum period. However, CPHIV regardless of IPA exposure type and CHEU without IPA exposure remain at a disadvantage and will benefit from intervention to support their growth.

Abbreviations: 3TC = lamivudine, ART = antiretroviral therapy, ARV = antiretroviral drug, cART = combination ART, CHEU = children HIV exposed uninfected, CHUU = children HIV unexposed uninfected, CI = confidence interval, CIPHER = collaborative initiative for paediatric hiv education and research, CPHIV = children with perinatally acquired HIV infection, HAZ = height-for-age z score, HIV = human immunodeficiency virus, IPA = in utero- and peripartum-antiretroviral, MTCT = mother-to-child transmission of HIV, PMTCT = prevention of MTCT, SD = standard deviation, sdNVP = single dose nevirapine, WHO = World Health Organization, WLWH = women living with HIV, ZDV = zidovudine.

Keywords: adolescents, antiretroviral therapy (ART), children, growth, HIV exposed uninfected, perinatal HIV infection, peripartum ART exposure, Uganda

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1. Introduction

Effective antiretroviral therapy (ART) during pregnancy and lactation has reduced mother-to-child transmission of human immunodeficiency virus (HIV) (MTCT) for children born to women living with HIV (WLWH).[1,2] Hence, the proportion of children born HIV-free despite in utero- and peripartum-antiretroviral (IPA) drug and HIV-exposure is the fastest growing demographic of HIV-affected individuals. Whether these children thrive developmentally in their long-term growth remains unknown. ART regimens used for prevention of MTCT in pregnant WLWH have been associated with developmental and neurological problems, and thus were reclassified from preferred to alternative in certain contexts depending on drug interaction concerns by the Health and Human Services, World Health Organization (WHO), or other such regulatory agencies.[3] WHO prevention of MTCT (prevention of MTCT [PMTCT]) guidelines, actual PMTCT coverage and exact IPA regimen used for PMTCT varied across HIV-treatment eras.[4] Specifically, ART prophylaxis using a single or a combination of ART drugs was the guideline in place prior to 2012; thereafter, combination ART (cART) for life in WLWH regardless of maternal CD4 cell-count (i.e., Option B+) was instituted.[5] Programmatically, the needed scale-up to be consistent with changes in guidelines varied by locale and importantly, cART was provided to the sickest pregnant WLWH while relatively healthier pregnant WLWH were provided prophylaxis. Some nucleoside reverse transcriptase inhibitors such as zidovudine and lamivudine (3TC) used for PMTCT and typically administered in combination with nevirapine or as part of cART, have been associated with acquired mitochondrial toxicity. Mitochondrial toxicity contributes to deoxyribonucleic acid alteration and increases the likelihood of impaired developmental trajectory.[6]

Epidemiologic data shows that frequency of adverse physical and mental health outcomes is high in HIV-affected populations throughout the life course[7–9] but the relationship of IPA exposure type to post-infancy developmental trajectory of HIV- and ART-exposed children and adolescents is under-explored. Height-for-age is among the most potent predictors of optimal brain health and typical cognitive development.[10] Further, growth deficits in childhood predict higher morbidity and diminished economic productivity in adulthood.[11] Studies have associated poor growth with poor academic outcomes, reduced lifelong earnings, higher child mortality and even intergenerational adverse effects on health and human capital.[12] Thus, understanding IPA-associated differences in growth trajectory is key to designing empirically informed interventions to mitigate stunting- a problem of high global health priority.

By virtue of ongoing HIV-related morbidity, growth in children with perinatally acquired HIV (CPHIV) is expected to be worse than in HIV-uninfected peers. For children HIV exposed uninfected (CHEU), the relative variation in long-term growth according to IPA exposure type compared to CHEU peers not exposed to any IPA or control children HIV unexposed and uninfected (CHUU) beyond early childhood is poorly elucidated, and available information is conflicting. Worse growth for CHEU relative to CHUU was found in 2 studies,[1,13] with a variation in growth outcomes based on type of in utero ART regimen exposure.[13] Specifically, in a study from Malawi, CHEU with in utero exposure to cART were shorter than CHEU exposed to zidovudine (ZDV) at 2 years old.[14] In another study of 562 newborns from four African countries, CHEU treated with lopinavir-ritonavir prophylaxis for a year, were growth delayed compared to CHEU peers treated with 3TC over the same interval. Long-term studies of IPA exposure type-related variations in height-for-age are few[13,15]; one of 2 available studies suggests that by 5 to 7 years of age, there was no difference in growth for CHEU that received lopinavir-ritonavir versus 3TC prophylaxis for 1 year.[13] However, the absence of a control group of CHUU limits scope of interpretation as comparison of growth relative to HIV unaffected and ART unexposed children was not possible.[13]

For both CPHIV and CHEU there may be important variations in long-term growth according to early life ART regimen exposure type. To contribute longer term data on growth trajectory of HIV- and ART- exposed children of pregnant WLWH and inform the current knowledge gap regarding possible variations in growth according to early life ART exposure, we test the hypothesis that long-term growth in HIV-exposed children will vary according to perinatal HIV status and maternal ART exposure type during pregnancy. We expect that CPHIV will experience less growth relative to CHEU and CHUU peers due to ongoing HIV-related morbidity. This information could guide adjunct interventions to improve long term growth in HIV and ART exposed children and targeting of such interventions to the most vulnerable children.

2. Methods

2.1. Participants and study context

The study included children born between the years 2000 and 2011 along with their adult caregivers enrolled as part of 2 year-long cohort studies. The first cohort included 300 (6–10 years old) children – that is, the collaborative initiative for paediatric hiv education and research (CIPHER) cohort, enrolled between March 15, 2017 and September 15, 2018. The second included 450 adolescents 11 to 18 years old – that is, the R21 cohort, enrolled between October 23, 2018 and November 11, 2019. CPHIV and CHEU were recruited by targeting HIV-positive adult patients in care a community health center in Kampala, Uganda. Potentially eligible HIV exposed children born in the health center were identified through the Early Infant Diagnosis registers and by direct communication with current adult PLWH in care. Lastly, CHUU were recruited from the general ward or referred to study team from the social networks of caregivers already enrolled into the study. The HIV status of both CHEU and CHUU at study enrollment was confirmed by rapid HIV diagnostic tests.

2.2. Screening, recruitment, eligibility confirmation, follow-up

Initial point of contact for study recruitment was the birth mothers' medical record and/or the current adult caregiver of potentially study eligible children. We targeted and screened potentially eligible CPHIV and CHEU using information from the antenatal registry and early infant diagnoses files in a primary healthcare center in urban Kampala, Uganda. Potentially eligible CHUU and some CHEU were recruited from the emergency department or through referral from the social network of already enrolled individuals. Children were identified for participation based on known perinatal HIV status along with their current adult (≥18 years) caregivers regardless of the current caregiver's HIV status. All participants were enrolled on a first-come first-served basis, but children recruited from the emergency department were given appointments for interview and study assessments when applicable health episode was completely resolved. Eligibility criteria for this study included: being a dependent child aged 6 to 18 years for whom HIV and ART exposure status (for index child and their birth mother) could be objectively verified via medical records during pregnancy and or birth. Because objective retrospective ascertainment of child and birth mother's HIV status and in utero/peripartum ART exposure was necessary to classify the primary study exposure in this study. We enrolled only children born in medical facilities that had documented information regarding participation in the prevention of MTCT services. Each enrolled child was followed

for 12 months or until loss to follow-up with study assessments at months 0, 6, and 12.

3. Ethical approval

Research protocols for respective cohorts were reviewed and approved by the research ethics review boards of Michigan State University (IRB Protocol numbers: 16-828 and 205), Makerere University College of Health Sciences, School of Medicine (Protocol REC REF numbers: 2017-017 and 2018-099), and the Uganda National Council for Science and Technology (Protocol #s: SS4378 and HS 2466). All caregivers gave written informed consent, and children provided assent or consent for study participation.

4. Measures

4.1. Outcome: height-for-age

Children's height-for-age relative to WHO growth standards[16] was assessed at enrollment, and each follow-up period. For this analysis, follow-up was complete for 6 to 10-year-old children. Follow-up was ongoing for 11 to 18 years old adolescents with included data collected on or before May 30, 2021. At each time point, height (in cm) was measured by specifically trained study nurse or medical officer in triplicate on a wall-mounted stadiometer with fixed measuring tape, a firm base and a movable headboard. At measurement children were bare feet, standing with heels of both feet together, their toes pointing slightly forward, their body weight evenly distributed on both feet and the back of their feet, calves, bottom, upper back and back of head in contact with the vertical board wall. Height was recorded as the distance from the ground to a mark against vertical board (to the nearest 0.1 cm) made by pulling down the movable headboard to rest directly on the top of a child's head. Entries were managed in Research Electronic Data Capture software. Strategies to assure data quality and limit implausible entries included entry range restriction, with values <85 cm and values >220 cm automatically flagged in Research Electronic Data Capture Software[17,18] for review. In addition, we required 3 assessments with the mean of available measures analyzed as height in each interval. For analytic purposes, growth was analyzed as continuous height-for-age z score (HAZ) calculated using WHO AnthroPlus macro (Geneva, Switzerland). Secondarily, we quantified relative prevalence of children at risk for stunting (i.e., HAZ < −1.5) or stunted (i.e., HAZ < −2) according to HIV-status and IPA type.

4.2. Primary determinant: in utero/peripartum ART (IPA) exposure type

Child IPA exposure was established from medical records, namely: birth mother's ART treatment card, antenatal or early infant diagnosis registers for CPHIV and CHEU who were exposed to one of four IPA types. These included: natural history condition – that is, infant not exposed to any antiretroviral drug in utero or postpartum (i.e., no IPA), intrapartum prophylactic single-dose nevirapine with/without ZDV (sdNVP ± AZT), intrapartum prophylactic sdNVP + AZT + 3TC that is, sdNVP + AZT + 3TC, and cART, including at least 2 antiretroviral drug classes. The primary determinant was ultimately analyzed as a 9-category covariate in which 8 IPA exposure categories (i.e., 4 for CPHIV and 4 for CHEU) were compared to CHUU (reference).

4.3. Other covariates & potential confounders

Caregiver sociodemographic factors and psychosocial factors that have potential to influence growth trajectory through the caregiving environment[19–22] were measured via standardized questionnaires and adjusted for in multivariable analyses.

1.4.3. Sociodemographic factors. Biological sex (male vs female) and chronologic age (in years) were defined for caregivers and dependent children. For children, developmental stage was defined as pre-adolescent (<11 years) versus adolescent (≥11 years). Education was defined as years of formal education completed by adult caregivers.

2.4.3. Relationship to current caregiver & vital status of birth mother. The relationship between child and caregiver pair was reported by primary caregiver and ultimately classified as: biological parent, non-parent blood relative or non-relative. At baseline, whenever the presenting primary caregiver was other than the biological mother, specific follow-up question probed for the reason biological mother was absent. Response options included: mother not living, travel, illness or other. Biological mother was coded as dead, only if death was provided as reason for absence of birth mother.

3.4.3. Caregiving context. Five contextual variables (caregiver adversity, social standing, functioning in caregiving role, depressive & anxiety symptoms, and functional social support) that influence the developmental outcomes of dependent children was measured in the caregivers using validated, translated and culturally adapted versions of standardized questionnaires. Variables were individually adjusted in multivariable models as potential confounders of IPA-related differences in child growth.

1) Lifetime adversity – defined as numeric sum of 13 adverse events experienced (score = 1) or not (score = 0) over the life course per the stressful life events questionnaire.[23]
2) Perceived social standing (lowest = 1–highest = 10) was assessed using MacArthur scale of subjective social standing[24–26] and analyzed as low (<1st tertile), medium (1st ≤ medium ≤ 2nd tertile) or high (>2nd tertile) per our sample's distribution of caregivers' self-ranking of their social standing in their community.
3) Functioning in caregiving role (lowest = 1 to highest = 120) was measured using an adapted version of the Barkin index of maternal functioning scale.[27,28]
4) Caregiver depressive and anxiety symptoms were measured using 15 and 10 items from the Hopkins Symptom Checklist-25.[29,30]
5) Social support was measured as the summed score of 8 questions[31] adapted from the Duke-UNC functional Support Questionnaire,[32] in which adult HIV-affected and HIV-unaffected caregivers expressed agreement with statements about their ability to access wanted emotional, monetary, and physical support resources.

5. Statistical analysis

This secondary analysis within CPHIV and CHEU status included four IPA exposure groups that were compared with CHUU as the primary determinant. We estimated the minimum detectable effect size with 80% power using a 2-sided test at 0.05 level of significance. The minimum detectable effect size varied according to the available number of children within IPA groups in the cohort. Specifically, compared to the 238 CHUU, this study has 80% power to detect effect sizes of ≥0.3 for HIV-group comparisons; and ≥0.4 for comparison of CHEU/CPHIV groups without IPA exposure versus CHUU. The detectable effect size was larger (>0.5) in the comparisons of other IPA categories (i.e., SdNVP ± AZT, SdNVP ± AZT + 3TC, and cART).

Means, standard deviations (SD), frequencies, and percentages were estimated within categories of IPA exposure. Unadjusted differences in child and caregiver sociodemographic factors, and HAZ measures according to child IPA and HIV status were evaluated using t tests for continuous variables and X^2 tests for categorical variables. Multivariable linear mixed effects models were fit for 3 repeated measures of HAZ in relation to

IPA/HIV exposure, with the adjustment for caregiver factors (sex, age, education, functioning in caregiving role, and lifetime adversity) to control for factors other than IPA that may influence a child's growth. Two random effects were specified: one for nesting of children within the same caregiver, and another for nesting of repeated measures over time within the child. Our analytic method used Statistical Analysis Software's (SAS v 9.4) PROC MIXED which robustly estimates IPA differences in growth with the assumption that unobserved follow-up data is missing at random in relation to IPA type and growth. Potential for varied IPA-growth association according to HIV treatment era, was explored via sensitivity stratified according to calendar year of birth (2000–2008 vs 2007–2011).

The least square means of HAZ values (average over time) were estimated from these models for the IPA exposure levels, and their differences from CHUU were estimated with 95% confidence intervals (CIs). Because HAZ was standardized using WHO reference with standard deviation of 1 for the global population, the differences between least square means reflected the effect sizes, and Cohen cutoffs of <0.2, ≥0.2 to <0.5, and ≥0.5 (i.e., small, moderate, and large effect, respectively) were used to quantify clinical importance. In practice, effect size thresholds for judging clinical importance and onward impact on health policy are guided by several factors including: population level impact, prevalence of the underlying condition, and availability of tools for mitigation. In this case, growth faltering/stunting is highly prevalent around the world, it is the strongest modifiable predictor of adverse neurodevelopment and in absence of intervention exacts large direct and intergenerational costs across the human life-course.[12] Hence, consistent with prior research on modifiable determinants of child developmental outcomes,[33–35] effect sizes of ≥0.2 are interpreted as being of moderate clinical importance. All statistical analysis was implemented in Statistical Analysis Software (v.9.4) (SAS Institute Inc., Cary, NC).

6. Results

6.1. Adult caregiver characteristics

A total of 512 caregivers along with 728 dependent children were included in the present study. Of the enrolled adults, 222 (43.4%), 140 (27.3%), and 150 (29.3%) were primary caregivers of CPHIV, CHEU and CHUU respectively. The average caregiver had 6 years of education with years of education. Caregiver perceived social standing, acute stress and lifetime adversity levels varied according to perinatal HIV status and IPA exposure groups (Table 1). Caregivers of CHUU had the highest level of education, and subjective social standing was highest among caregivers of CPHIV exposed to cART in the peripartum period. There were no differences across perinatal HIV status and ART exposure groups with respect to caregiver reported social support, depressive and anxiety symptoms. Among HIV-positive current caregivers, 37(~11%) cared for CHUU and have lived with HIV for significantly fewer years ($P = .004$, Table 1) compared to caregivers of other children, however there was no difference in duration of HIV infection for caregivers of CPHIV and CHEU, with means across IPA regimens ranging from 11.4 to 12.6 years (Table 1).

Medical record regarding HIV-disease stage and immune status in pregnancy was available for 72.6% (n = 228) of the birth mothers with HIV-infection. Of these, 85.9% (n = 203) had WHO class 1 or 2 HIV disease, the average pregnancy CD4 cell count was 290 cells/μL (SD = 206) and the average number of pregnancies (including index child's) was 2.9 (SD = 1.8). Further, 34.6% (n = 80) of pregnant women with HIV were on first-line cART for their own health for a mean duration of 1.84 (SD = 1.51) years (Table S1, Supplemental Digital Content, http://links.lww.com/MD/I332).

By enrollment, birth mother was deceased for 14.9% (n = 109) of children with birthmother death highest among CPHIV (n = 68 or 27.4%) relative to CHEU (n = 23 or 9.5%) or CHUU (n = 18 or 7.6%). With respect to relationship with current caregiver, most children were in care of biological parents (n = 503, 69.3%) or non-parent blood relative (n = 185, 25.5%); only 38 (5.2%) were in care of non-family adult caregivers. Across perinatal HIV status and early ART exposure types, caregiver sex, average age, caregiver reported economic dependency and functioning in caregiving role were similar (Table 1).

6.2. Child characteristics

Of the 757 initially enrolled, a total of 728 children including 293 from the CIPHER cohort study and 435 from the adolescent R21 cohort study were included in the analysis. Analytic sample included 390 girls and 338 boys of average age 11 years were enrolled (Fig. 1). Among CHEU height-for-age relative to WHO reference ranged from 0.4 to 1.1 z scores lower relative to WHO reference with substantial variation according to IPA type. The lowest height at baseline (1.2–1.3 z scores lower) was evident among CPHIV with little variation by IPA type. Across perinatal HIV status and early ART exposure types, average age and sex distribution of children were similar (Table 1).

6.3. cART status and immunologic status of CPHIV

Of the 222 CPHIV enrolled, 97% were currently on cART for their own health. Average CD4 cell count being 1281 (SD = 657) in the CIPHER cohort and 578 (SD = 250) in the adolescent R21 cohort. Further, 51% of the CPHIV in the CIPHER cohort and 24% of CPHIV in the adolescent cohort were stably virologically suppressed. Extensive information regarding child immunologic and HIV-treatment parameters for CPHIV has been published elsewhere.[36]

6.4. Growth according to HIV & IPA exposure type over 12 months

Ugandan children in this study on average grew at relative disadvantage compared to WHO reference population at all study intervals. Across perinatal HIV groups, HAZ ranged from −1.21 (SD = 1.04) for CPHIV to a high of −0.77 (SD = 1.12) for CHUU at baseline. Mean baseline height-for-age varied significantly across early antiretroviral drug (ARV) exposure types ($P < .001$). At enrollment, average HAZ of CHUU (mean = −0.77, SD = 1.11) was not different from that of children exposed to cART in utero in the peripartum period (mean = −0.71, SD = 1.18) (Table 2). At baseline, the prevalence of stunting (i.e., HAZ < −2.0) among CHUU, CHEU and CPHIV respectively was 10.9%, 14.5%, and 20.2%. Among CHEU, the prevalence of stunting at baseline according to IPA exposure status was 17.5% for intrapartum sdNVP ± AZT, 8.3% for intrapartum sdNVP + AZT + 3TC, 2% for cART, and 22.3% for children with no ART exposure (Table 1).

6.5. Relationship between growth, peripartum HIV status and early ART exposure

Median follow-up duration was 12 months with missing information driven by ongoing follow-up of 11 to 18 years old children. In all, 85% and 73% of participants enrolled at baseline were respectively evaluated at follow-up months 6 and 12. Adjusted for time, birth cohort, caregiver demographics (sex, age, education) and caregiving contextual factors (functioning in caregiving role, perceived social standing, lifetime adversity), head-to-head comparison of growth according to perinatal HIV status groups demonstrated that CPHIV were growth disadvantaged (mean difference = −0.36, 95% CI: −0.54, −0.18), whereas CHEU had similar growth (mean difference = −0.02;

Table 1

Baseline description of study base with respect to type of in utero/peripartum ART exposure and perinatal HIV status.

	CPHIV (N = 248)				CHEU (N = 242)				CHUU (N = 238)*	
	sdNVP ± AZT	sdNVP + AZT + 3TC	In utero cART	No peripartum ARV	sdNVP ± AZT	sdNVP + AZT + 3TC	In utero cART	No peripartum ARV	Not HIV or ARV exposed	*P* value
	n (%)/ mean (SD)	n (%)/ mean (SD)	n (%)/ mean (SD)	n (%)/ mean (SD)	n (%)/ mean (SD)	n (%)/ mean (SD)	n (%)/ mean (SD)	n (%)/ mean (SD)	n (%)/mean (SD)	t/χ^2
Child characteristics	N = 61	N = 27	N = 24	N = 136	N = 40	N = 48	N = 51	N = 103	N = 238	
Female child [n (%)]	39 (63.9)	14 (51.8)	12 (50.0)	68 (50.0)	25 (62.5)	27 (56.3)	28 (54.9)	56 (51.5)	124 (52.1)	.721
Age (yr, mean SD)	12 (3.7)	11 (4.0)	11 (4.3)	12 (3.8)	12 (3.9)	12 (3.2)	10 (3.2)	11 (3.6)	11 (3.6)	.120
Calendar yr of birth (cohort)										
2007–2011 (CIPHER)	23 (37.7)	10 (37.0)	10 (41.7)	57 (41.9)	17 (42.5)	12 (25.0)	25 (49.0)	42 (40.8)	97 (40.8)	.553
2000–2008 (R21)	38 (62.3)	17 (63.0)	14 (58.3)	79 (58.1)	23 (58.1)	36 (75.0)	26 (51.0)	61 (59.2)	141 (59.2)	
Immune metrics|PWLWH†										
CD4 cell count (uL/mL)	357 (164)	269 (118)	279 (201)	260 (152)	305 (173)	398 (242)	266 (211)	362 (219)	–	
HIV disease stage mean (minimum, maximum)	1.8 (1, 3)	1.4 (1, 2)	1.8 (1, 3)	1.7 (1, 3)	1.8 (1,3)	1.1 (1,2)	1.8 (1,3)	1.8 (1.3)	–	
Biological mother deceased (n, %)	16 (26.2)	6 (22.2)	5 (20.8)	41 (30.4)	5 (12.5)	5 (10.4)	4 (7.8)	9 (8.7)	18 (7.6)	<.001
Relationship to current caregiver										.132
Biological child	41 (67.2)	19 (70.4)	15 (62.5)	81 (60.0)	26 (65.0)	35 (72.9)	34 (66.7)	76 (73.7)	157 (66.5)	
Blood relative	18 (29.5)	4 (14.8)	7 (29.2)	50 (37.0)	13 (32.5)	10 (20.8)	15 (29.4)	25 (24.3)	61 (25.9)	
Non-relative	2 (3.3)	4 (14.8)	2 (8.3)	4 (3.0)	1 (2.5)	3 (6.3)	2 (3.9)	2 (3.9)	18 (7.6)	
Growth metrics										
HAZ (mean, SD)	–1.2(1.0)	–1.2 (1.3)	–1.3 (0.9)	–1.2 (1.0)	–1.0 (1.0)	–0.9 (0.9)	–0.4 (1.2)	–1.1 (1.3)	–0.8 (1.1)	.002
Stunted (HAZ < –2, n, %)	10 (16.4)	8 (29.6)	7 (29.2)	25 (18.4)	7 (17.5)	4 (8.3)	1 (2.0)	23 (22.3)	26 (10.9)	.001
At-risk (HAZ ≤ –1.5, n, %)	20 (32.8)	11 (40.7)	11 (45.8)	56 (41.2)	14 (32.5)	13 (27.1)	7 (13.7)	37 (35.9)	59 (24.5)	.003
Current caregiver characteristics	N = 57	N = 24	N = 22	N = 119	N = 27	N = 37	N = 30	N = 46	N = 150	
Age (yr, mean, SD)	35.9 (9.9)	33.6 (9.3)	35.1 (11.7)	38.3 (11.2)	40.7 (11.5)	43.0 (11.1)	38.7 (12.1)	40.8 (12.1)	36.6 (10.7)	.005
Female (n, %)	44 (77)	21 (91.3)	20 (90.9)	103 (88.8)	23 (85.2)	32 (86.5)	26 (92.9)	41 (91.1)	137 (92.0)	.957
Yr of formal education (mean, SD)	7.0 (3.5)	6.7 (3.3)	8.1 (4.0)	6.5 (3.9)	6.6 (2.7)	5.2 (3.0)	5.9 (3.8)	5.2 (3.3)	7.3 (4.0)	.003
HIV+ (n, %)	44 (77.2)	17 (70.8)	15 (75.0)	78 (67.8)	25 (92.6)	33 (89.2)	28 (93.3)	45 (97.8)	36 (24.2)	<.001
Yr lived with HIV| HIV+	12 (4.2)	11 (4.0)	12 (5.6)	12 (5.7)	13 (5.0)	12 (5.6)	12 (4.9)	13 (5.9)	9 (6.1)	.031
Sociodemographic factors										
Has own income (n, %)	44 (77.2)	20 (83.3)	18 (85.7)	87 (73.7)	22 (81.5)	29 (78.4)	22 (73.3)	34 (73.9)	113 (75.3)	.935
Depends on another for financial support (n, %)	30 (52.6)	12 (50.0)	16.9 (72.7)	69 (59.0)	13 (48.2)	21 (56.7)	17 (56.7)	27 (58.7)	92 (61.7)	.727
Caregiving context: Psychosocial, stress & behavioral factors										
Caregiver functioning (mean, SD)	59 (10.0)	61 (9.5)	58 (5.6)	57 (9.1)	57 (9.9)	59 (9.1)	58 (9.5)	57 (8.1)	57 (10.4)	.256
Perceived social standing (mean, SD)	3.3 (1.23)	3.1 (3.1)	4.3 (1.5)	3.4 (1.5)	2.9 (1.5)	3.1 (1.2)	3.5 (1.8)	3.4 (1.5)	3.6 (1.4)	.045
Lifetime adversity score (mean, SD)	1.5 (2.0)	3.0 (2.8)	2.2 (2.3)	2.0 (2.0)	2.4 (2.6)	3.2 (3.4)	3.2 (2.7)	2.5 (2.4)	2.1 (2.1)	.005
Recent life stress (mean, SD)	7.7 (4.1)	9.0 (2.8)	7.7 (3.4)	7.5 (3.7)	8.3 (4.5)	8.5 (3.4)	9.0 (3.1)	7.4 (3.5)	8.3 (3.9)	.299
Anxiety score (mean, SD)	7.4 (7.0)	8.3 (6.9)	8.9 (6.5)	7.2 (6.3)	8.9 (7.2)	8.7 (6.7)	9.3 (6.6)	9.3 (6.8)	7.8 (7.1)	.580
Social support (mean, SD)	11.1 (6.0)	11.5 (4.9)	11.3 (5.2)	11.8 (4.9)	13.0 (5.0)	12.1 (3.5)	11.7 (5.6)	10.6 (5.2)	11.3 (5.0)	.733
Depressive symptoms (mean, SD)	9.2 (8.5)	10.5 (7.9)	11.8 (9.4)	9.7 (8.7)	11.2 (9.3)	11.7 (9.2)	13.3 (8.3)	11.7 (7.3)	10.5 (8.2)	.445
Ever alcohol use (n, %)	24 (42.1)	12 (50.0)	7 (31.8)	56 (47.1)	13 (48.2)	19 (51.4)	11 (36.7)	26 (56.5)	48 (32.0)	.059

3TC = lamivudine, ART = antiretroviral therapy, cART = combination ART, CHEU = children HIV exposed uninfected, CPHIV = children with perinatally acquired HIV infection, HAZ = height-for-age, HIV = human immunodeficiency virus, SD = standard deviation, WLWH = women living with HIV.

† Among children born to women living with HIV during index child's pregnancy (i.e. CHEU and CPHIV) information regarding CD4 and World Health Organization (WHO) disease stage was obtainable from medical records for 113 unique mothers (in the CIPHER cohort) and 124 mothers in the R21 cohort. Across cohorts, this metric was available for birthmothers of 124 CPHIV and 109 CHEU.

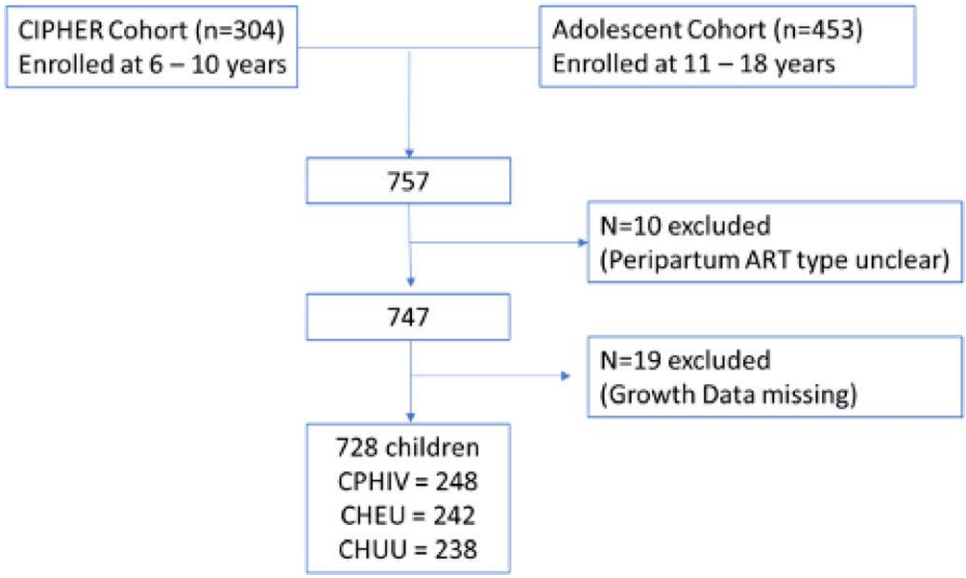

Figure 1. Study base for early ART and growth association. ART = antiretroviral therapy, CPHIV = children with perinatally acquired HIV infection, CHEU = children HIV exposed uninfected, CHUU = children HIV unexposed uninfected.

Table 2

Height-for-age *z* score (HAZ) over 12 months among 728 Ugandan children 6 to 18 years old according to perinatal HIV status and peripartum antiretroviral regimen-exposure type.

	Month 0		Month 6		Month 12		Time-averaged
HIV status & ART exposure type	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**Mean (SD)**
CPHIV	248	−1.21 (1.04)	217	−1.09 (1.08)	176	−1.09 (1.00)	−1.14 (1.03)
No ARV in utero or peripartum	136	−1.18 (1.05)	119	−1.10 (1.01)	100	−1.07 (0.90)	−1.10 (1.23)
sdnvp+/−AZT	61	−1.20 (0.99)	50	−1.19 (1.06)	37	−1.31 (0.93)	−1.24 (0.99)
sdnvp+ AZT + 3TC	27	−1.23 (1.33)	25	−1.04 (1.25)	22	−1.00 (1.15)	−1.11 (0.98)
cART	24	−1.33 (0.87)	20	−1.04 (1.40)	16	−0.86 (1.45)	−1.11 (1.21)
CHEU	242	−0.91 (1.19)	218	−0.86 (1.17)	178	−0.80 (1.21)	−0.87 (1.20)
No ARV in utero or peripartum	103	−1.12 (1.29)	94	−1.06 (1.25)	82	−1.01 (1.37)	−1.05 (1.31)
SdNVP+/−AZT	40	−1.04 (0.96)	38	−1.05 (0.96)	28	−1.13 (1.03)	−1.03 (1.03)
SdNVP + AZT + 3TC	48	−0.88 (0.95)	40	−0.89 (0.98)	30	−0.82 (0.86)	−0.87 (0.93)
cART	51	−0.42 (1.21)	46	−0.29 (1.14)	40	−0.24 (1.04)	−0.34 (1.14)
CHUU	238	−0.77 (1.12)	208	−0.79 (0.99)	180	−0.72 (1.02)	−0.77 (1.04)
Total (within time intervals)	728	−0.96 (1.13)	638	−0.91 (1.09)	531	−0.87 (1.10)	

3TC = lamivudine, ARV = antiretroviral drug, ART = antiretroviral therapy, cART = combination ART, CPHIV = children perinatally HIV infected, CHEU = children HIV exposed uninfected, CHUU = children HIV unexposed, uninfected, HAZ = height-for-age, HIV = human immunodeficiency virus, SD = standard deviation, sdNVP+/−AZT = single dose nevirapine with or without zidovudine, sdNVP + AZT + 3TC = single dose nevirapine with zidovudine and lamivudine.

95% CI: −0.21, 0.18) relative to CHUU by 6 to 18 years old. Further disaggregation of according to early ART exposure type of HIV/ART exposed children affirms the overall relationship for comparison of CPHIV to CHUU as similar magnitude of growth deficit was realized regardless of IPA type, although the relationship was significant only for CPHIV without any ARV exposure in early life (mean difference = −0.41, 95% CI: −0.72, −0.11) and for CPHIV with peripartum sdNVP + AZT (mean difference = −0.39, 95% CI: −0.67, −0.11) exposure. Relative to CHUU, CPHIV exposed to peripartum cART (mean difference = −0.40, 95% CI: −0.87, 0.07) and those exposed to SdNVP + AZT + 3TC (mean difference = −0.32, 95% CI: −0.78, 0.13) had moderately lower growth, although these associations were not statistically significant (Table 3).

The association between type of IPA exposure and long-term growth for CHEU relative to CHUU was more variable in direction. Specifically, CHEU without any ARV in utero or peripartum had growth disadvantage (mean difference = −0.27, 95% CI: −0.52, −0.01) while CHEU exposed to cART had a growth advantage (mean difference = 0.40; 95% CI: 0.08, 0.71) of moderate clinical importance relative to CHUU. Lastly, relative to CHUU, there was no association of growth of: CHEU exposed to SdNVP ± AZT (mean difference = −0.16, 95% CI: −0.46, 0.14) and CHEU exposed to SdNVP + AZT + 3TC (mean difference = 0.08, 95% CI: −0.20, 0.35) in the peripartum period (Table 3, Fig. 2).

6.6. Other determinants of height-for-age: Calendar year of birth & contextual factors

Compared to younger cohort of children 6 to 10 years old born between the years 2007 and 2011, height-for-age was lower (mean difference = −0.55, 95% CI: −0.71, −0.38) for the older cohort of 11 to 18 years children who were born between the years 2000 and 2008 and this difference in growth according to cohort/calendar year of birth amounted to large clinical importance. In addition, having a surviving (difference = 0.27, 95% CI: 0.06, 0.47) versus deceased birthmother positively influenced growth trajectory whereas having a caregiver with low versus high education (difference = −0.24, 95% CI: −0.46, −0.02),

Table 3

Time-averaged association between perinatal HIV status, early ART exposure type, select demographic and psychosocial covariates and height-for-age by 6 to 18 years of age*.

		Unadjusted association		Multivariable model 1*		Multivariable model 2†	
Peripartum ART & perinatal HIV status	N	Unadjusted mean HAZ (SE)	Standardized mean difference relative to CHUU (95% CI)	Adjusted mean HAZ (SE)	Standardized mean difference relative to CHUU (95% CI)	Adjusted mean HAZ (SE)	Mean difference relative to CHUU (95% CI)
CPHIV	248	−1.18 (0.06)	−0.39 (−0.57, −0.21)	−1.23 (0.08)	−0.36 (−0.54, −0.18)	−1.04 (0.09)	−0.30 (−0.48, −0.11)
No ARV in utero or peripartum	136	−1.17 (0.08)	−0.37 (−0.58, −0.17)	−1.03 (0.09)	−0.30 (−0.50, −0.09)	−1.00 (0.11)	−0.28 (−0.48, −0.07)
SdNVP ± AZT	61	−1.20 (0.12)	−0.40 (−0.69, −0.15)	−1.04 (0.13)	−0.31 (−0.59, −0.04)	−1.02 (0.15)	−0.32 (−0.58, −0.02)
SdNVP + AZT + 3TC	27	−1.15 (0.23)	−0.35 (−0.85,0.09)	−1.05 (0.22)	−0.32 (−0.78, 0.13)	−1.05 (0.23)	−0.32 (−0.78, 0.13)
cART	24	−1.19 (0.21)	−0.39 (−0.84, 0.02)	−1.14 (0.23)	−0.41 (−0.88, 0.06)	−1.12 (0.23)	−0.40 (−0.87, 0.07)
CHEU	242	−0.89 (0.07)	−0.10 (−0.29, 0.10)	−0.89 (0.08)	−0.02 (−0.21, 0.18)	−0.78 (0.10)	−0.06 (−0.23, 0.14)
No ARV in utero or peripartum	103	−1.08 (0.13)	−0.28 (−0.56, −0.003)	−0.98 (0.12)	−0.25 (−0.51, 0.01)	−0.97 (0.14)	−0.27 (−0.52, −0.00)
SdNVP ± AZT	40	−1.03 (0.14)	−0.23 (−0.55, 0.07)	−0.90 (0.14)	−0.17 (−0.47, 0.14)	−0.88 (0.15)	−0.16 (−0.46, 0.14)
SdNVP + AZT + 3TC	48	−0.88 (0.13)	−0.08 (−0.37, 0.19)	−0.65 (0.13)	0.08 (−0.19, 0.36)	−0.64 (0.14)	0.08 (−0.20, 0.35)
cART	51	−0.40 (0.15)	0.40 (0.07, 0.73)	−0.33 (0.15)	0.40 (0.09, 0.71)	−0.31 (0.15)	0.41 (0.10, 0.71)
CHUU	238	0.80 (0.07)	Ref	−0.73 (0.06)	Ref	−0.72 (0.09)	Ref
Calendar yr of birth (cohort)							
2007–2011 (CIPHER)	293	−0.60 (0.06)	Ref	−0.58 (0.07)	Ref	−0.61 (0.10)	Ref
2000–2008 (R21)	441	−1.20 (0.05)	−0.59 (−0.75, −0.44)	−1.14 (0.07)	−0.56 (−0.73, −0.40)	−1.15 (0.09)	−0.55 (−0.71, −0.38)
Caregiver formal education (yr)							
0–4	356	−1.06(−0.05)	−0.24 (−0.46, −0.02)	−0.97 (0.07)	−0.17 (−0.41, 0.06)	−0.98 (0.09)	−0.18 (−0.42, 0.05)
5–9	241	−0.87 (0.07)	−0.05 (−0.28, 0.19)	−0.85 (0.08)	−0.05 (−0.28, 0.19)	−0.86 (0.10)	−0.05 (−0.29, 0.18)
11–17	131	−0.82 (0.10)	Ref	−0.80 (0.11)	Ref	−0.80 (0.12)	Ref
Current caregiver's perceived social standing							
Low	421	−1.06 (0.05)	−0.34 (−0.54, −0.13)	−1.02 (0.06)	−0.29 (−0.50, −0.07)	−1.04 (0.09)	−0.29 (−0.50, −0.08)
Medium	173	−0.92 (0.07)	−0.20 (−0.43, 0.04)	−0.84 (0.09)	−0.11 (−0.34, 0.13)	−0.86 (0.11)	−0.11 (−0.35, 0.12)
High	140	−0.72 (0.09)	Ref	−0.73 (0.10)	Ref	−0.75 (0.11)	Ref
Caregiver's relationship to child							
Biological parent	486	−0.90 (0.05)	Ref	–	–	−0.85 (0.08)	Ref
Non-parent blood relative	207	−1.11 (0.07)	−0.21 (−0.38, −0.04)	–	–	−0.93 (0.09)	−0.08 (−0.28, 0.11)
Non-relative	38	−1.05 (0.18)	−0.15 (−0.52, 0.22)	–	–	−0.85 (0.08)	−0.01 (−0.38, 0.36)
Vital status (birth mother)							
Dead	112	−1.19 (0.10)	Ref	–	–	−0.91 (0.12)	Ref
Alive	619	−0.92 (0.04)	0.27 (0.06, 0.47)	–	–	−0.86 (0.08)	0.04 (−0.20, 0.28)

3TC = lamivudine, ART = antiretroviral therapy, ARV = antiretroviral drug, cART = combination ART, CHUU = children HIV unexposed uninfected, CI = confidence interval, CPHIV = children with perinatally acquired HIV infection, HAZ = height-for-age, HIV = human immunodeficiency virus.

*Results are from multivariable linear mixed effects model adjusted for time, recruitment as part of the adolescent versus school-aged cohort study, caregiver's (sex, age, education, functioning in caregiving role, perceived social standing, lifetime adversity). In the absence of time-trends in peripartum ART relationship to growth, time-averaged associations are presented. † This model is further adjusted for relationship of current caregiver to study child (biological parent, non-parent biological relative versus non-blood relative) and vital status (alive vs. dead) of birth mother.

a non-parent versus parent primary caregiver (difference = –0.21, 95% CI: –0.38, –0.04) and caregiver-reported low versus high perceived social standing (difference = –0.34, 95% CI: –0.54, –0.13) predicted growth deficits of modest to moderate clinical importance in unadjusted models. With the exception of calendar year of birth and perceived social standing, mutual adjustment for IPA exposure history, caregiver demographic and caregiving context in multivariable models attenuated the association between height-for-age and the socio-demographic and caregiving contextual factors – that is, caregiver education, parent versus non-parent relationship to study child and survival status of biological mother of dependent child – and these relationships each became statistically insignificant and relatively small in clinical importance (Table 3, Fig. 2).

The analyses restricted to developmental stage (6–10 vs 11–18 years), which corresponds to era of birth, confirmed the growth disadvantage of CPHIV as a group and that of CPHIV without any ARV in the peripartum period relative to CHUU regardless of age. However, peripartum SdNVP ± AZT exposure associated growth deficit relative to CHUU was of large clinical importance among pre-adolescent CPHIV (mean difference = –0.65, 95% CI: –0.96, –0.35) only. Similarly, cART associated growth advantage was evident among pre-adolescents (mean difference = 0.62, 95% CI: 0.13, 1.10) but not among adolescent children (mean difference = –0.15, 95% CI: –0.54, 0.23) born between 2000 and 2008. Further, the growth disadvantage of CHEU without peripartum ARV exposure versus CHUU was evident in the adolescent cohort and absent in the school-aged cohort (Table 4).

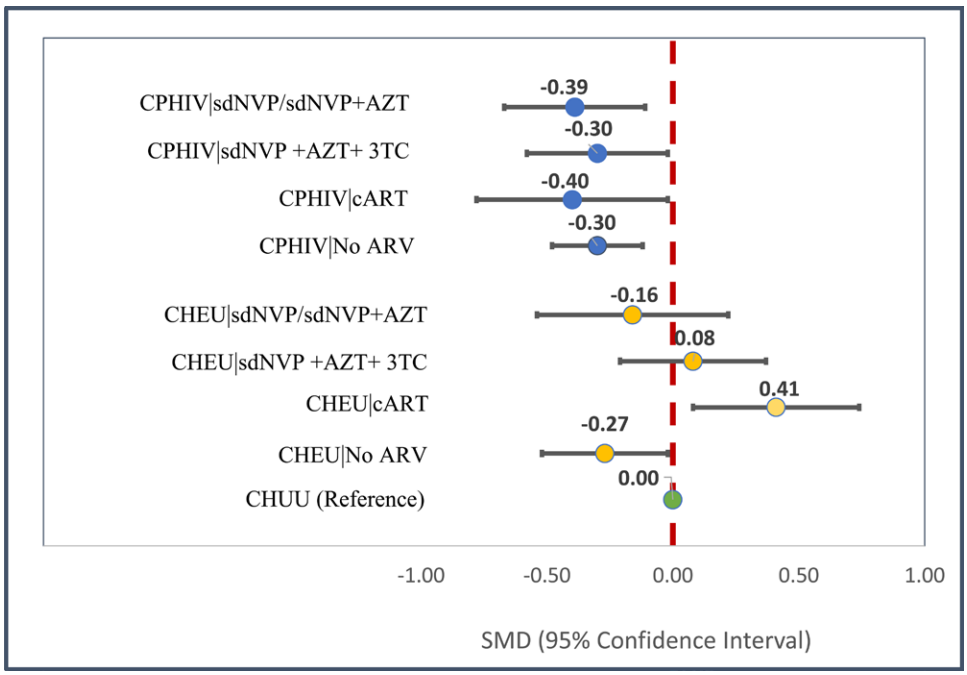

Figure 2. Early ART-associated differences in height-for-age among children born to HIV+ pregnant women from Uganda relative to children HIV unexposed uninfected at 6 to 18 years old. ART = antiretroviral therapy.

Table 4

Time-averaged association between early ART exposure type and growth according to early ART exposure type and child's developmental stage.

	School-age cohort (calendar yr of birth: 2007–2011)		Adolescent cohort (calendar yr of birth: 2000–2008)	
	Adjusted mean HAZ (SE)	Mean difference from CHUU (95% CI)	Adjusted mean HAZ (SE)	Mean difference from CHUU (95% CI)
Early ART exposure status				
CPHIV	–1.02 (0.11)	**–0.45 (–0.71, –0.20)**	–1.30 (0.08)	**–0.27 (–0.50, –0.04)**
sdNVP ± AZT	–1.23 (0.14)	**–0.65 (–0.96, –0.35)**	–1.18 (0.18)	–0.15 (–0.54, 0.23)
sdNVP + AZT + 3TC	–0.81 (0.41)	–0.24 (–1.06, 0.59)	–1.34 (0.24)	–0.32 (–0.83, 0.19)
In utero cART	–0.95 (0.35)	–0.37 (–1.07, 0.33)	–1.43 (0.25)	–0.40 (–0.93, 0.12)
No ARV in utero or peripartum	–0.99 (0.14)	**–0.41 (–0.72, –0.11)**	–1.32 (0.11)	**–0.30 (–0.56, –0.03)**
CHEU	–0.47 (0.12)	0.10 (–0.19, 0.39)	–1.14 (0.09)	–0.12 (–0.37, 0.13)
sdNVP ± AZT	–0.78 (0.17)	–0.20 (–0.60, 0.21)	–1.13 (0.22)	–0.11 (–0.57, 0.36)
sdNVP + AZT + 3TC	–0.48 (0.23)	0.10 (–0.38, 0.58)	–0.94 (0.14)	0.08 (–0.24, 0.40)
In utero cART	0.04 (0.23)	**0.62 (0.13, 1.10)**	–0.82 (0.16)	0.21 (–0.15, 0.56)
No ARV in utero or peripartum	–0.62 (0.17)	–0.05 (–0.42, 0.32)	–1.40 (0.16)	**–0.38 (–0.74, –0.02)**
CHUU	–0.58 (0.11)	Ref	–1.02 (0.09)	Ref

Adjusted for time, caregiver sex, caregiver age, caregiver education, caregiver functioning, caregiver lifetime adversity; Early ART* adolescent, $P = .3934$; early ART*HIV status, $P = .220$. Bolded values represent differences that were statistically significant.

3TC = lamivudine, ART = antiretroviral therapy, ARV = antiretroviral drug, cART = combination ART, CHEU = children HIV exposed uninfected, CHUU = children HIV unexposed uninfected, CI = confidence interval, CPHIV = children with perinatally acquired HIV infection, HAZ = height-for-age, HIV = human immunodeficiency virus.

7. Discussion

In line with our study hypothesis, we found growth deficit for CPHIV in comparison with CHUU peers. This finding confirms previously reported observations of growth disadvantage for CPHIV when compared to CHUU and adds to growing evidence that deficits among CPHIV infants and children <2 years old are sustained through childhood and adolescent years of life.[37] Further disaggregation according to IPA exposure type suggests that the long-term growth disadvantage of CPHIV persists regardless of early ART exposure type and observed differences were of moderate clinical importance.

The growth for Ugandan CHEU and CHUU was similar by age 6 to 18 years. This finding is consistent with findings from the CHER trial among seven to nine years old CHEU and CHUU and among 6 to 12 years old Zambian CHEU versus CHUU.[38,39] Beyond these 2 studies, the bulk of comparative growth information available is from studies of children <5 years old, and conclusions based on these studies were inconsistent. A total of 3 studies – including 2 studies of young children from South Africa provide corroborating evidence of growth parity for CHEU relative to CHUU by 2 to 3 years old.[15,40] In a large multinational study of over 1500 CHEU from four countries in South Africa, length for age *z* score was similar for CHEU exposed to maternal cART and those whose mothers were not on cART by 24 months of age.[15] Similar to our findings, maternal cART in that study was associated with lower risk of being underweight. In the other study of children from birth to 3 years old, HAZ was comparable for CHEU and CHUU.[40] Furthermore, in a nationwide cohort study of nearly 3000 Danish children <5 years old CHEU are smaller at birth, but the disadvantage in growth parameters decreased over time, and CHEU achieved relative growth parity with CHUU beyond 18 months old.[41] In contrast with these reports, in a larger set of 10 studies from Africa, worse growth for HIV-and ART-exposed infants and toddlers within 2 years of life was seen relative to CHUU peers.[1,14,42–46] Our findings based on CHEU versus CHUU comparison at 6 to 18 years align with recent observations in older children and suggests that previously observed growth deficits for CHEU relative to CHUU may not persist into school-age and adolescent years of life.

By further disaggregating growth among CHEU according to early ART exposure type, we provide greater resolution on this question for children born in an era when access to antiretroviral drugs for pregnant HIV-positive women varied in availability, quality, and quantity. In line with our study hypothesis, long-term growth of CHEU indeed varied according to IPA exposure type. Specifically, we found that after controlling for child relationship to caregiver, birth mother's HIV status, calendar time, maternal demographic (age, sex, education), psychosocial and caregiving context (perceived social standing, functioning in caregiving role, lifetime adversity), CHEU exposed to intrapartum SdNVP ± AZT and CHEU with no IPA exposure had long-term growth disadvantage of modest to moderate clinical importance, whereas CHEU exposed to SdNVP + AZT + 3TC had growth comparable to CHUU. Interestingly, CHEU with peripartum cART exposure had superior growth to CHUU peers by 6 to 18 years old. This relationship is noteworthy in part because vast majority of children in this study were born at a time when maternal access to cART was predicated on being sufficiently immune compromised. Information abstracted from the antenatal registry record of HIV+ birth mother shows that median duration of cART use among HIV+ mother was 1.84 years and mean CD4 count was 290 (SD = 206) cells/UL obtained during gestation period for study child. Hence, despite eligibility based on advanced disease, pregnant HIV+ birth mothers had the benefit of significant immune restoration, which likely improved the gestational environment for their unborn child and contributed to better postnatal growth. This long-term positive association between peripartum cART and growth among children born between 2000 and 2008 is encouraging and suggests that previously reported early cART-associated growth deficit for CHEU at 2 years old[14] may not persist into school-age and adolescent years of life.

Results from this study also suggests that CHEU exposed to only intrapartum SdNVP ± AZT had poorer growth relative to CHEU peers whose HIV+ biological mothers were on cART during pregnancy. In contrast with our finding, in one study among Ugandan and Malawian children at 4 to 5 years old,[47] growth was similar for CHEU exposed to cART in utero relative to CHEU peers exposed to ZDV (i.e., SdNVP ± AZT).[47] An important difference between that study and ours that may explain this difference is that, calendar years of birth was 2013 to 2014 in that study (i.e., well into the Option B+ era), versus 2000 to 2011 in our study which spanned more eras of the HIV epidemic.

Few studies of African children have gone beyond gross perinatal HIV group comparisons to report on associations between nature of maternal ART and growth in children beyond early childhood. In a study of children from Botswana, in utero cART exposure predicted worse growth in comparison with CHEU peers exposed to ZDV/AZT over 24 months.[14] In 2 studies among infants from Malawi and South Africa, there was no difference in linear growth over 18 months for infants whose mothers were exposed to lifelong ART relative to CHUU peers.[48,49] Because growth is a predictor of cognitive function, adult morbidity and overall productivity, the sustained growth disadvantage evident for CPHIV and for some CHEU depending on their type of IPA exposure is a public health challenge that warrants intervention targeted at the most vulnerable children.

8. Strengths & limitations

Strengths of this study lie in its prospective cohort design and large sample size including school-aged and adolescent children whose perinatal HIV status and early life ART exposure type were established objectively via medical records. A further strength is the availability of wider scope of comparative groups including a natural history group of HIV-exposed but not ARV exposed children and various forms of IPA exposures within and across perinatal HIV status groups. This feature provided resolution beyond perinatal HIV status to examine and quantify nuances in the relationship of IPA regimen to growth within respective HIV groups. Therefore, the results of this study expand the scope of available information in this area and suggests that in addition to CPHIV regardless of peripartum ART exposure status, CHEU without any IPA exposure may be at elevated risk of stunting. However, once broken down by types of IPA exposures, some subgroup sizes – specifically SdNVP ± AZT, SdNVP + AZT + 3TC and cART, were relatively small in this study. This precluded the reliable evaluation of differences in growth for these groups relative to CHUU and precluded reliable assessment of interactions between IPA exposure type and cohort of birth. Further strength lies in this study having data regarding birth mother's vital status at enrollment, the relative health of pregnant HIV+ women during index pregnancy (e.g., WHO classification and CD4 cell count) and availability of rich socio-demographic, psychosocial and caregiving context variables that were controlled for and provided context for interpreting the results of this study.

The observational design of this investigation limits inference from this study to associations between IPA regimen and long-term growth. In addition, we are unable to exclude the potential for survival bias in population of children of WLWH that survive to be included in this study. Furthermore, important temporal trends must be carefully considered in the interpretation of findings from this study. Specifically, children and adolescents included in this study were born during a time of limited ART availability followed by substantial changes in ART standard

of care for pregnant WLWH. This meant newborns were allocated whatever IPA was available to WLWH per guidelines in place during their era of pregnancy/birth. For oldest children in this study to WLWH, exposure to cART was contingent on their birthmother's having sufficiently low CD4. In contrast, contemporary CHEU are exposed to cART during all periods of gestation and postnatally during breastfeeding. Therefore, the associations described reflect the growth experience of surviving children born to WLWH between 2000 and 2011. It may not reflect the growth experience of HIV/ART exposed children in different HIV eras – including the current test and treat era of the HIV pandemic.

9. Conclusions

The finding that growth for CHEU with IPA regimen exposure was not different from CHUU or could be better (if cART-based IPA) than CHUU by 6 to 18 years old is encouraging though ultimately, hypothesis generating given power limitations within IPA categories. Nevertheless, these data suggests that CHEU may thrive with respect to growth by school-age and adolescent years if provided the benefit of cART in early life. Growth deficits persisted for CPHIV regardless of IPA exposure type and for CHEU with no IPA exposure and these subgroups represent pockets of ongoing developmental disadvantage with estimated differences in the range of moderate to large in clinical importance. These data suggest that supportive interventions designed to improve growth in these vulnerable HIV-exposed children will be especially beneficial to CPHIV and CHEU with no IPA exposure.

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