Comparative growth of children who are HIV-exposed and uninfected with those who are HIV-unexposed and uninfected at age 1 and 2 years in South Africa: a prospective cohort study

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Summary

Background The effects of maternal HIV infection and antiretroviral therapy (ART) on growth of children who are HIV-exposed and uninfected (CHEU) are uncertain. We aimed to explore the association between in utero exposure to maternal HIV and child growth in the context of ART for all pregnant women living with HIV regardless of CD4 count.

Methods We compared growth at 1 and 2 years of age between CHEU and children who are HIV-unexposed and uninfected (CHUU) in a prospective cohort study (INTERBIO-21st), conducted in Soweto, South Africa, with recruitment of pregnant women between 21 May 2013 and 21 December 2015. Length-for-age (LAZ), weight-for-age (WAZ), weight-for-length (WLZ) and head circumference-for-age (HCAZ) Z-scores, based on the World Health Organization (WHO) Child Growth Standards, were compared longitudinally using age-specific and mixed linear regression. Prevalence of stunting, underweight, wasting and overweight were compared at 1 and 2 years.

Findings At 1 and 2 years of age, 398 (143 CHEU, 255 CHUU) and 286 (82 CHEU, 204 CHUU) children, respectively, were followed up. CHEU and CHUU had LAZ and WAZ scores considerably below the WHO standardised median at 1 year (CHEU: mean (SD) LAZ −1.13 (1.39), WAZ −0.29 (1.33); CHUU: LAZ −0.87 (1.33), WAZ −0.15 (1.20)) and 2 years (CHEU: LAZ −1.00 (1.24), WAZ −0.52 (1.05); CHUU: LAZ −0.94 (1.33), WAZ −0.34 (1.19)), whereas WLZ scores were above the median at year 1 only (CHEU 0.34 (1.27), CHUU 0.42 (1.28). There were no statistically significant differences in growth between CHEU and CHUU, although there was a trend to lower LAZ (adjusted mean difference [aMD] −0.19 [95% CI: −0.43, 0.06]), WAZ (aMD −0.09 [95% CI: −0.30, 0.15]), WLZ (aMD −0.06 [95% CI: −0.30, 0.18]) and HCAZ (aMD −0.14 [95% CI: −0.36, 0.08]) scores in CHEU. Stunting prevalence was high in both groups at both timepoints (1 year CHEU 29.3% [95% CI: 22.4%, 37.3%], CHUU 19.4% [95% CI: 15.0%, 24.8%]; 2 years CHEU 18.8% [95% CI: 11.7%, 28.7%], CHUU 20.5% [95% CI: 15.5%, 26.6%]). The risk of stunting, underweight and wasting was higher in CHEU at 1 year, but not significant in analyses adjusted for maternal age, height, weight, nulliparity, smoking, alcohol use, socioeconomic status, education, marital status, child sex and age (stunting adjusted odds ratio [aOR] 1.56 [95% CI: 0.91, 2.68], underweight aOR 1.69 [95% CI: 0.71, 4.03], wasting aOR 3.64 [95% CI: 0.62, 31.2]), and risks were similar between the groups at 2 years (stunting aOR 0.77 [95% CI: 0.35, 1.61], underweight aOR 1.01 [95% CI: 0.34, 2.70], wasting aOR 0.93 [95% CI: 0.11, 5.39]). At 2 years, CHEU had lower risk of overweight (adjusted OR 0.12 [95% CI: 0.00, 0.89]).

Interpretation No significant differences in growth were observed between CHEU and CHUU children up to 2 years. The prevalence of stunting was high in both groups. Key limitations of this study include limited data on maternal ART and infant breastfeeding, which may have introduced residual confounding. Future studies should aim to identify children that are most at risk of growth impairment to enable the development of targeted interventions for optimising growth and healthy development.

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Research in context

Evidence before this study

We searched three electronic bibliographic databases (MEDLINE, Embase, Global Health) and three clinical trials databases (Cochrane Library, WHO ICTRP clinical trials database, and ClinicalTrials.gov) for studies on growth of children who are HIV-exposed and uninfected (CHEU), compared to children who are HIV-unexposed and uninfected (CHUU), published between 1 January 1996 and 13 January 2025, using a comprehensive search strategy structured around the terms "child" AND "HIV" AND ("growth" OR "weight" OR "length" OR "height"). Among the few studies of CHEU with documented exposure to maternal antiretroviral therapy (ART), most found that CHEU had lower length-for-age Z-scores (LAZ) and a higher risk of stunting. Results on weight-for-age Z-scores (WAZ), underweight and overweight were mixed, and no study reported differences in weight-for-length Z-scores (WLZ) or wasting between CHEU and CHUU. Studies published prior to the introduction of universal ART, in which participants were exposed to no antiretroviral drugs, zidovudine monotherapy, or triple therapy, depending on ART guidelines at the time of study and maternal CD4 count, showed similar results in terms of a trend towards lower LAZ scores and higher risk of stunting, varied results on WAZ scores and underweight, and generally no or small differences in WLZ scores or wasting.

Added value of this study

Our study assesses growth outcomes in a well characterised cohort of South African CHEU and CHUU who were recruited early during foetal life and followed up for 2 years, in the era when ART was recommended for all pregnant women living with HIV. Our findings show a high prevalence of stunting in both CHEU and CHUU up to 2 years, and no significant differences in Z-scores in CHEU compared to CHUU, although there was a trend towards slightly lower Z-scores in CHEU. CHEU had a lower risk of being overweight at 2 years, compared to CHUU.

Implications of all the available evidence

CHEU may have slightly lower growth Z-scores compared to CHUU during the crucial first 1000 days from conception to 2 years, though differences are small and not consistently statistically significant. Reassuringly, CHEU do not appear at higher risk of wasting compared to CHUU. The evidence is limited on the risk of overweight in CHEU and CHUU, and considering the rising dual burden of malnutrition (combined stunting and overweight), this is an important area to explore further. Published studies often contain limited information on maternal ART, and are based on small sample sizes. Future research should consistently report data on maternal ART during pregnancy. In addition, a systematic review and meta-analysis may address the limitation of small individual studies and help identify potential differences in growth outcomes between CHEU and CHUU.

Introduction

Over the past two decades, global scale-up of universal antiretroviral therapy (ART) for pregnant women living with HIV has substantially reduced mother-to-child HIV transmission,[1] leading to greater numbers of children who are HIV-exposed and uninfected (CHEU). In 2023, 84% of the 1.2 million women living with HIV who became pregnant received ART antenatally, the majority of whom gave birth to CHEU infants. The same year, UNAIDS estimated there were 16.1 million CHEU and adolescents aged 0–15 years globally, 91% of whom live in sub-Saharan Africa.[2]

Although CHEU are HIV-negative, they may be affected by antenatal exposure to maternal HIV and ART, resulting in impaired growth and other adverse outcomes such as increased mortality and higher infectious morbidity during infancy, childhood and adolescence, compared to children who are HIV-exposed and uninfected (CHUU).[3] Delayed growth is associated with long-term consequences including health-related outcomes such as cardiovascular disease, hypertension and chronic diseases of nutrition, as well as broader socioeconomic impacts including delayed cognitive development, lower educational attainment and reduced economic productivity in adulthood.[4] In South Africa, where an estimated 4.3 million children under 15 years were CHEU in 2023,[2] growth delays in this population could have substantial long-term public health and socioeconomic implications.

Growth of CHEU is affected by a complex interplay of factors, including health related factors such as maternal HIV disease stage, adverse perinatal outcomes and duration of breastfeeding,[5,6] and broader determinants such as food security and socioeconomic status.[7,8] Studies on growth of CHEU show heterogeneous results. Several studies conducted both before

and after the introduction of universal ART during pregnancy have shown slightly delayed growth among CHEU compared with CHUU, with modest differences in Z-scores typically ranging between 0.2 and 0.5 standard deviations (SD).[3,6,9–14] However, other studies have found no significant differences.[3,5,12,15] Most studies have been conducted in low- and middle-income countries, but studies from high-income settings have reported similar heterogeneity, showing either small growth delays among CHEU[11] or no differences between groups.[15]

We aimed to explore the association between in utero exposure to maternal HIV and child growth in the context of ART for all pregnant women living with HIV regardless of CD4 count. We hypothesised that CHEU may have delayed growth compared to CHUU, potentially related to biological, treatment-related or socioeconomic pathways linked to exposure to maternal HIV. We therefore compared the growth of CHEU and CHUU at 1 and 2 years of age, using data from a well characterised prospective pregnancy cohort in the South African arm of the INTERBIO-21st Study.[16]

Methods

Study design and participants

Pregnant women were recruited during the first trimester from antenatal care services at Chris Hani Baragwanath Academic Hospital in Soweto, South Africa, between 21 May 2013 and 21 December 2015. Inclusion criteria included black South African, residing in Soweto, ≥18 years old, body mass index (BMI) less than 35.0 kg/m^2, naturally conceived singleton pregnancy, and gestational age <14^{+0} weeks at first visit. Exclusion criteria included multiple pregnancy, foetal abnormalities, epilepsy, type 1 diabetes, and intellectual or physical disability. After enrolment, women were followed up every 5 ± 1 weeks during pregnancy and at delivery; their children were followed up at 1 and 2 years.

To maximise retention of study participants, study staff formed relationships and developed trust with participating pregnant women during follow-up visits throughout pregnancy and at delivery. Study staff conducted home visits 10 days after delivery, when the mother was invited to visit the research centre, where additional follow-up visits were described. Participants were invited to follow-up appointments via telephone, with home visits to update contact information where required.

South African HIV guidelines at the time recommended routine HIV testing at the first antenatal appointment and immediate initiation of efavirenz-based ART as the first-line treatment regimen in those found to be living with HIV.[17] At the time of the study, lifelong ART was only recommended for women living with HIV with a CD4 count <350, whereas women living with HIV with a CD4 count above 350 stopped ART when breastfeeding ceased.

The study received ethical approval from the Oxfordshire Research Ethics Committee "C" (reference 08/H0606/139), the University of Oxford Tropical Research Ethics Committee (reference 1008-13), and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (references M241064, M120524 and M130905). All participants provided written informed consent at enrolment. Participants were reimbursed ZAR 150 for travel and their time at each visit to the research centre as per the Human Ethics Research Committee guidelines at the time. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Data collection

At enrolment, gestational age <14^{+0} weeks was confirmed by transabdominal ultrasound scan (Philips HD-9, Philips Ultrasound, Bothell, WA, USA). Data were collected on HIV status, socioeconomic characteristics, medical, gynaecological and obstetric history, drug history, smoking and use of alcohol from medical records and confirmed during participant interviews conducted in English, isiZulu, isiXhosa or Sesotho, as appropriate. Women not known to be living with HIV were routinely offered an HIV test. During pregnancy follow-up visits any changes in health status were documented. For women living with HIV, permission was sought to collect additional information from medical records on clinical stage of HIV disease, ART use, ART regimens and timing of initiation.

Information about newborn HIV status, determined before hospital discharge, was collected from medical records. A newborn was considered a child who was exposed to HIV if the mother was recorded as living with HIV at any appointment during pregnancy or at delivery.

Children were seen for scheduled follow-up visits at 1 and 2 years of age at a dedicated study site at the University of the Witwatersrand. At each follow-up appointment at age 1 and 2 years, detailed information was obtained from the mother about the child's health, medical history, and hospitalisations. The child's weight, length, and head circumference were measured following World Health Organization (WHO) protocols.[18] At each follow-up visit, the child's HIV status was determined from medical records, the Road to Health card, which documented data on routine HIV tests for HIV exposed children at 6 weeks of age, 10 weeks of age, 6 weeks after cessation of breastfeeding and at 18 months of age.

Newborn anthropometric measures were obtained by trained study staff, ideally within 12 h of birth (and no later than 24 h), as well as at 1 year and 2 years follow-up appointments, using an electronic scale

(Seca, Hamburg, Germany) for birthweight (sensitivity of 10 g up to 20 kg) and a specially designed Harpenden infantometer (Chasmors Ltd, London, UK) for recumbent length. The equipment was calibrated twice weekly. Head circumference was measured using a metallic non-extendable tape (Chasmors Ltd, London, UK). The quality control measures required the trained anthropometrists to take and record all measures twice independently and compare their values with the maximum allowable differences: newborn weight, 50 g; length, 7 mm; and head circumference, 5 mm. If the difference between the two measures exceeded these values then both observers independently repeated that measurement a second time and, if necessary, a third time.[19]

Study size

This is a secondary analysis of data collected at a single study site that participated in the international, multicentre, cohort study INTERBIO-21st.[20] Supplementary Tables S1 and S2 summarise the minimum effect sizes that could be detected with 80% power and a significance level of $p < 0.05$, given existing participant numbers at each timepoint. WHO has not published any formal definitions of minimal clinically important differences for anthropometric Z-scores. However, since Z-scores represent standard deviation units, differences in Z-scores can be interpreted using Cohen's *d* convention for standardised effect sizes, which defines small, moderate and large differences as a difference of 0.2, 0.5 and 0.8 SD, respectively.[21]

Statistical methods

Data processing

To ensure internal consistency, two repeated independent measures that differed by more than 7 mm for length, 50 g for weight or 5 mm for head circumference were excluded, in line with WHO methods.[22] For the remaining duplicate measures, the average of the measures was used.

Standardised length-for-age (LAZ), weight-for-age (WAZ), weight-for-length (WLZ) and head circumference-for-age (HCAZ) scores were calculated based on the WHO Child Growth Standards,[23] calculated using the R package 'whoanthro'.[24] In accordance with WHO guidance, measurements were excluded if they exceeded the following thresholds: LAZ <–6 or >6 standard deviations (SD), WAZ <–5 or >5 SD, WLZ < –6 or >5 SD, HCAZ <–5 or >5 SD.

A household wealth index was constructed using principal components analysis of an 11-item asset ownership score, and participants were categorised into wealth quintiles based on the first principal component.

Missing outcome data was <2.5% across outcomes. Most covariates had no missingness, and only one variable had >5% missingness (maternal parity, 6.3%). Based on this, we felt that multiple imputation of missing data was not necessary.

Descriptive statistics

Participant characteristics were summarised, stratified by HIV exposure status (CHEU vs. CHUU) and by retention in study. Differences between groups were assessed using Pearson's chi-square test and student t test or Wilcoxon rank test, as appropriate.

Linear regression analyses

Associations between HIV-exposure and continuous anthropometric outcomes (LAZ, WAZ, WLZ and HCAZ) were assessed separately at 1 and 2 years using unadjusted and adjusted linear regression models. Models were adjusted for maternal age, height, weight, nulliparity, smoking, alcohol use, socioeconomic status, education, marital status, child sex and age. These covariates were identified based on a directed acyclic graph (Supplementary Fig. S1).

Mixed linear regression models were used to analyse repeated measures based on combined 1 and 2 year data. First, a minimally adjusted model was constructed, which adjusted for the time of measurement (at 1 or 2 years). Second, a fully adjusted model was constructed, including all variables listed above. Third, an interaction term between HIV exposure and time was added to the fully adjusted model, to assess whether the strength of the association between HIV exposure and growth may have been different at 1 year compared with 2 years.

We assessed model assumptions for all linear regressions by inspecting histograms and Q–Q plots of residuals to check for normality, and plots of residuals vs. fitted values to check for homoscedasticity.

Logistic regression analyses

The proportion of CHEU and CHUU who had stunting (LAZ < –2 SD), underweight (WAZ < –2 SD), wasting (WLZ < –2 SD) or overweight (WLZ > 2 SD) were compared using unadjusted and adjusted logistic regression models. These analyses were done separately at 1 year and 2 years because the repeated measures analyses did not converge.

Sensitivity analyses

We conducted several sensitivity analyses.

First, we applied inverse probability weighting to the fully adjusted age-specific and mixed linear regression models, and to the fully adjusted age specific logistic regression models, to account for potential bias due to differential loss to follow-up of CHUU compared to CHEU children. We estimated the probability of inclusion in the analytic sample using logistic regression, in a prediction model that included the baseline characteristics that differed significantly between the groups that were retained and lost to follow-up. We removed the least significant variables sequentially until all remaining predictors were statistically significant at $p < 0.05$. This final model was used to generate weights

that were then applied to the fully adjusted linear and logistic regression models.

Second, since we hypothesised that breastfeeding and adverse perinatal outcomes (low birth weight [LBW, birth weight <2500 g], preterm birth [PTB, <37 weeks' gestation] or small for gestational age [SGA, <10th centile INTERGROWTH-21st newborn size standard[25]]) might lie on the causal pathway between antenatal HIV exposure and child growth, these variables were not adjusted for in the main analyses. In the sensitivity analyses each potential mediator was added separately to the fully adjusted mixed linear regression model, to assess the impact of adjusting for that covariate on the association between antenatal HIV-exposure and each anthropometric Z-score.

Third, we assessed the robustness of our findings by repeating the final mixed linear regression model in three sets of restricted analyses limited to: a) children born at term (37–42 weeks' gestation), not SGA, and exclusively breastfed on discharge from the labour ward, b) children who attended both follow-up appointments, and c) CHEU known to have been exposed to efavirenz-based ART during pregnancy.

Fourth, we assessed whether there was effect modification of the child's sex on growth outcomes, by adding an interaction term between HIV exposure and sex in the final mixed linear regression model.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participant characteristics

In total, there were 578 live-born infants in the cohort, all of whom were not living with HIV based on HIV test at birth and were eligible for inclusion (Fig. 1). After excluding 13 children who acquired HIV between birth and age 2 years, 565 children were retained. Among these, 444 (78.6%) children attended at least one follow-up appointment. At 1 and 2 years, 398 (143 CHEU, 255 CHUU) and 286 (82 CHEU, 204 CHUU) children, respectively, were seen for follow-up; of these, 240 (76 CHEU, 164 CHUU) were seen at both timepoints (Fig. 1).

Table 1 summarises the maternal and child characteristics. Compared to mothers without HIV, those living with HIV were older, less likely to complete secondary education, be nulliparous, or be from a higher wealth quintile. Maternal overweight or obesity (BMI >25) was common in both groups (94/149 [63%] of women living with HIV, 192/295 [65%] of women without HIV) (Table 1).

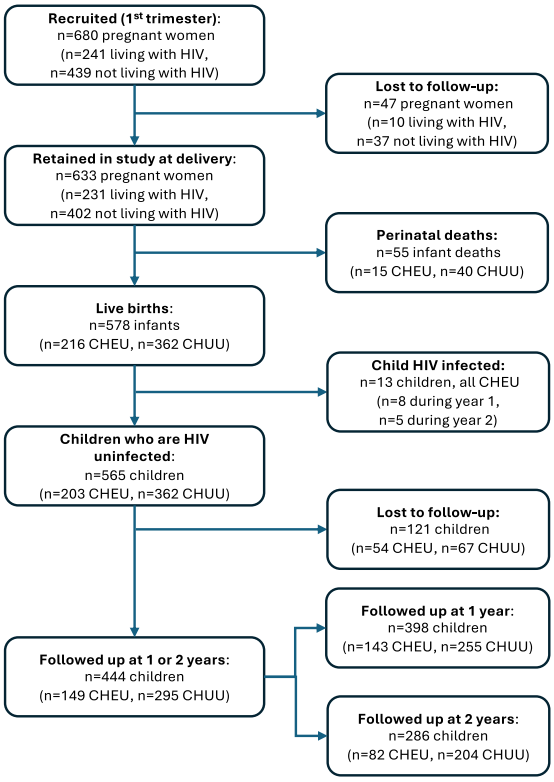

Fig. 1: Flow diagram of included participants. Number of participants included in the study from recruitment of pregnant women through to follow-up at 2 years. CHEU: children who are HIV-exposed and uninfected; CHUU: children who are HIV-unexposed and uninfected; HIV: human immunodeficiency virus.

Data on timing of HIV diagnosis were available for 39/149 (26.2%) women living with HIV; 17 (44%) of these were diagnosed prior to conception, while 22 (56%) were diagnosed during pregnancy (18 in the first trimester) (Supplementary Table S3). Data on timing of ART initiation were available for 69/149 (46.3%) women living with HIV. ART was initiated prior to conception in 28/69 (41%) women, while 40/69 (58%) started ART during pregnancy (31 in the first trimester), and 1/69 (1%) after birth. Most of the women received efavirenz-based ART (65/68 [96%]), while 2/68 (3%) received other triple therapy regimens and one participant (1%) received zidovudine monotherapy.

The prevalence of adverse perinatal outcomes was similar in CHEU and CHUU (LBW: 26/147 [18%] CHEU vs. 52/292 [18%] CHUU, p = 0.98; PTB: 25/149 [17%] CHEU vs. 42/295 [14%] CHUU, p = 0.48; SGA: 30/147 [20%] CHEU vs. 46/292 [16%] CHUU, p = 0.22) (Table 2). CHEU were less likely to be exclusively breastfed (79/149 [53%] CHEU vs. 239/293 [82%] CHUU), and more likely to be exclusively

Characteristic	Overall, N = 444	Women living with HIV or CHEU, N = 149	Women not living with HIV or CHUU, N = 295	p-value
Maternal characteristics				
Age at delivery (years)	31 (26, 35)	33 (28, 37)	30 (26, 34)	<0.0001
Completed secondary education (≥12 years)	332 (75%)	96 (64%)	236 (80%)	0.0003
Smoking during pregnancy	26 (5.9%)	10 (6.7%)	16 (5.4%)	0.59
Alcohol consumption during pregnancy	37 (8.3%)	15 (10%)	22 (7.5%)	0.35
BMI at baseline (kg/m^2)				0.73
≤18.5	7 (1.6%)	1 (0.7%)	6 (2.0%)	
18.5–24.99	151 (34%)	54 (36%)	97 (33%)	
25–29.99	174 (39%)	57 (38%)	117 (40%)	
≥30	112 (25%)	37 (25%)	75 (25%)	
Height at baseline (cm)	159 (155, 163)	158 (155, 163)	159 (155, 163)	0.97
Weight at baseline (kg)	68 (59, 76)	67 (59, 74)	68 (59, 76)	0.81
Nulliparous	60 (14%)	11 (7.7%)	49 (18%)	0.0045
Unknown	28	6	22	
Married or cohabiting	179 (40%)	53 (36%)	126 (43%)	0.15
Occupation				0.44
Not working	56 (13%)	23 (15%)	33 (11%)	
Other	217 (49%)	70 (47%)	147 (50%)	
Working	171 (39%)	56 (38%)	115 (39%)	
Wealth quintile				0.013
Quintile 1 (poorest)	81 (18%)	25 (17%)	56 (19%)	
Quintile 2	96 (22%)	44 (30%)	52 (18%)	
Quintile 3	77 (17%)	28 (19%)	49 (17%)	
Quintile 4	95 (21%)	31 (21%)	64 (22%)	
Quintile 5 (least poor)	95 (21%)	21 (14%)	74 (25%)	
Child characteristics				
Infant sex				0.92
Female	216 (49%)	72 (48%)	144 (49%)	
Male	228 (51%)	77 (52%)	151 (51%)	
Born by Caesarean section	257 (58%)	84 (56%)	173 (59%)	0.65
Gestational age at birth (weeks)	39 (37, 40)	38 (37, 39)	39 (37, 40)	0.60
Birth weight (g)	3005 (2,652, 3268)	3005 (2,620, 3252)	3015 (2,685, 3280)	0.63
Unknown	5	2	3	
Small for gestational age <10th centile	76 (17%)	30 (20%)	46 (16%)	0.22
Unknown	5	2	3	
Very small for gestational age < 3rd centile	18 (4.1%)	6 (4.1%)	12 (4.1%)	0.99
Unknown	5	2	3	
Preterm birth < 37 wks	67 (15%)	25 (17%)	42 (14%)	0.48
Very preterm birth < 32 wks	15 (3.4%)	4 (2.7%)	11 (3.7%)	0.57
Low birthweight < 2500 g	78 (18%)	26 (18%)	52 (18%)	0.98
Unknown	5	2	3	
Very low birthweight < 1500 g	10 (2.3%)	2 (1.4%)	8 (2.7%)	0.51
Unknown	5	2	3	
Congenital abnormality	2 (0.5%)	1 (0.7%)	1 (0.3%)	>0.99
Feeding mode at discharge from labour ward				<0.0001
Exclusive breastfeeding	318 (72%)	79 (53%)	239 (82%)	
Formula	94 (21%)	67 (45%)	27 (9.2%)	
Mixed	30 (6.8%)	3 (2.0%)	27 (9.2%)	
Unknown	2	0	2	

Median (interquartile range); n (%). BMI: body mass index; CHEU: children who are HIV-exposed and uninfected; CHUU: children who are HIV-unexposed and uninfected.

Table 1: **Maternal and child baseline characteristics.**

formula fed (67/149 [45%] CHEU vs. 27/293 [9.2%] CHUU), on discharge from the labour ward ($p < 0.0001$).

Fewer CHEU than CHUU were retained in the study (149/203 [71.6%] CHEU vs. 295/362 [82.6%] CHUU, $p = 0.0030$). Children who were lost to follow-

Continuous outcome	Unadjusted	Adjusted	Unadjusted	Adjusted	Minimally adjusted[a]	Fully adjusted[b]
	Year 1	Year 1	Year 2	Year 2	Repeated measures	Repeated measures
	MD (95% CI), p-value	Adjusted MD (95% CI), p-value	MD (95% CI), p-value	Adjusted MD (95% CI), p-value	MD (95% CI), p-value	MD (95% CI), p-value
Length-for-age Z-score	−0.26 (−0.54, 0.02), p = 0.065	−0.24 (−0.52, 0.04), p = 0.10	−0.06 (−0.40, 0.28), p = 0.74	0.01 (−0.33, 0.35), p = 0.97	−0.22 (−0.46, 0.03), p = 0.088	−0.19 (−0.43, 0.06), p = 0.13
Weight-for-age Z-score	−0.14 (−0.40, 0.12), p = 0.29	−0.08 (−0.34, 0.18), p = 0.55	−0.18 (−0.48, 0.12), p = 0.23	−0.06 (−0.36, 0.24), p = 0.69	−0.16 (−0.39, 0.08), p = 0.19	−0.09 (−0.33, 0.15), p = 0.48
Weight-for-length Z-score	−0.08 (−0.35, 0.18), p = 0.53	−0.04 (−0.31, 0.24), p = 0.80	−0.19 (−0.48, 0.11), p = 0.21	−0.08 (−0.39, 0.23), p = 0.60	−0.13 (−0.36, 0.10), p = 0.27	−0.06 (−0.30, 0.18), p = 0.61
Head circumference-for-age Z score	−0.18 (−0.41, 0.05), p = 0.12	−0.16 (−0.40, 0.07), p = 0.18	−0.24 (−0.52, 0.03), p = 0.081	−0.14 (−0.43, 0.14), p = 0.33	−0.18 (−0.39, 0.03), p = 0.091	−0.14 (−0.36, 0.08), p = 0.23
Binary outcome	**OR (95% CI), p-value**	**Adjusted OR (95% CI), p-value**	**OR (95% CI), p-value**	**Adjusted OR (95% CI), p-value**	**OR (95% CI), p-value**	**OR (95% CI), p-value**
Stunting	1.72 (1.06, 2.77), p = 0.027	1.56 (0.91, 2.68), p = 0.11	0.89 (0.45, 1.70), p = 0.74	0.77 (0.35, 1.61), p = 0.49	–	–
Underweight	1.72 (0.78, 3.79), p = 0.18	1.69 (0.71, 4.03), p = 0.23	1.09 (0.40, 2.65), p = 0.86	1.01 (0.34, 2.70), p = 0.98	–	–
Wasting	2.42 (0.53, 12.44), p = 0.25	3.64 (0.62, 31.2), p = 0.17	0.99 (0.14, 4.72), p > 0.99	0.93 (0.11, 5.39), p = 0.94	–	–
Overweight	0.88 (0.40, 1.84), p = 0.75	1.00 (0.43, 2.20), p > 0.99	0.08 (0.00, 0.61), p = 0.0082	0.12 (0.00, 0.89), p = 0.035	–	–
Stunting and overweight	0.36 (0.00, 4.45), p = 0.46	0.17 (0.00, 9.46), p = 0.35	0.49 (0.00, 6.12), p = 0.62	0.52 (0.00, 5.88), p = 0.65	–	–

Number of participants with available data for each outcome: Year 1: LAZ 140 CHEU, 252 CHUU; WAZ 142 CHEU, 253 CHUU; WLZ 140 CHEU, 250 CHUU; HCAZ 142 CHEU, 255 CHUU. Year 2: LAZ 80 CHEU, 200 CHUU; WAZ 82 CHEU, 202 CHUU; WLZ 80 CHEU, 199 CHUU; HCAZ 81 CHEU, 201 CHUU. CI: confidence interval; MD: mean difference; OR: odds ratio. [a]Adjusted for child age. [b]Adjusted for maternal age, height, weight, nulliparity, smoking, alcohol use, socioeconomic status, education, marital status, child sex and age.

Table 2: **Age-specific and repeated measures linear regression analyses of growth outcomes at 1 and 2 years.**

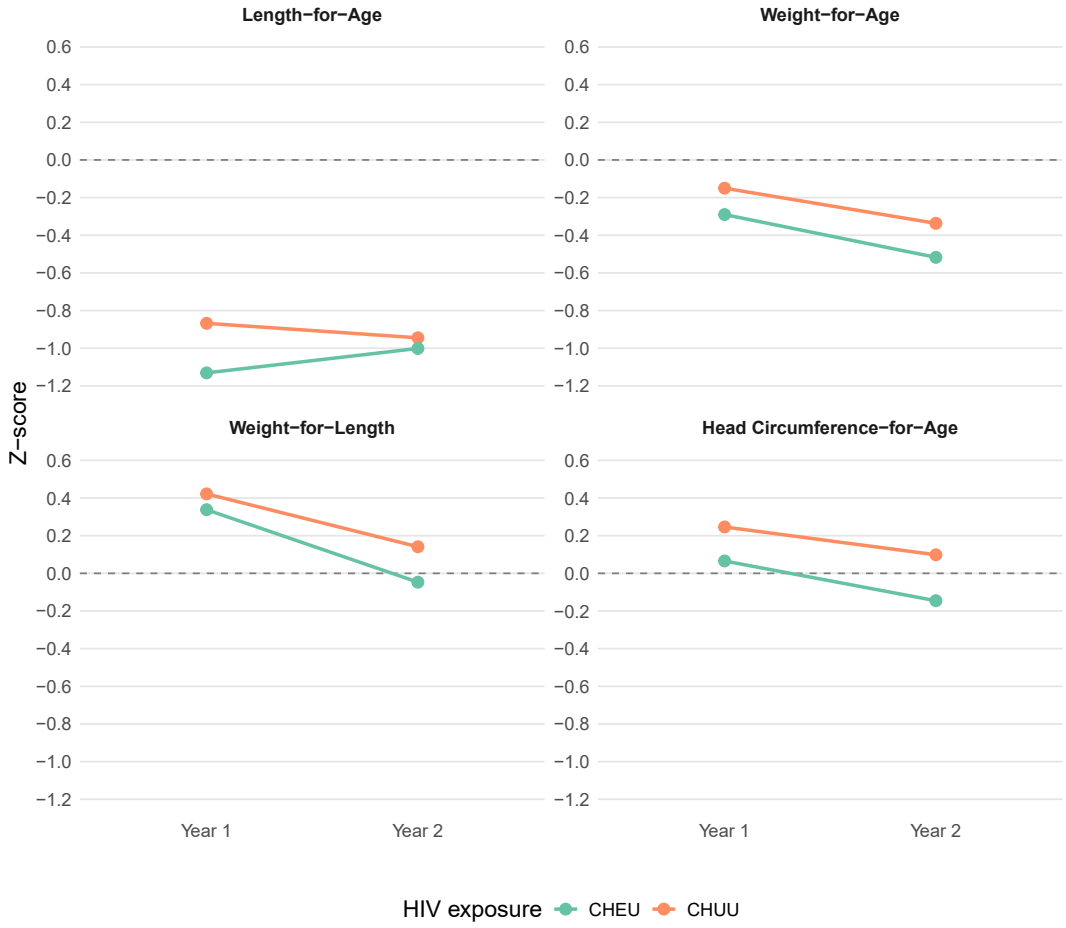

Fig. 2: Anthropometric Z-scores in CHEU and CHUU at 1 and 2 years. Mean Z-scores in CHEU and CHUU for length-for-age, weight-for-age, weight-for-length and head circumference-for-age at 1 and 2 years. Green: CHEU, orange: CHUU. CHEU: children who are HIV-exposed and uninfected; CHUU: children who are HIV-unexposed and uninfected; HIV: human immunodeficiency virus.

up had mothers who were less likely to have completed secondary education, were less likely from a higher wealth quintile, and had higher proportion of PTB and LBW, compared to those that were retained (Supplementary Table S4).

LAZ and stunting

Mean LAZ scores were below the WHO standardised median in both groups at 1 and 2 years (Fig. 2; Supplementary Table S5). There were no significant differences in LAZ scores at 1 year (adjusted mean difference [MD] −0.24 [95% confidence interval [CI]: −0.52, 0.04], p = 0.10), or 2 years (adjusted MD −0.01 [95% CI: −0.33, 0.35], p = 0.97) (Table 2). Mixed linear regression models showed no significant differences, although there was a trend towards lower LAZ scores in CHEU (fully adjusted MD −0.19 [95% CI: −0.43, 0.06], p = 0.13) (Table 2). At 1 year, the prevalence of stunting was 29% (41/140) in CHEU and 19% (49/252) in CHUU (Fig. 3). CHEU had a higher risk of stunting at 1 year in the unadjusted analysis (unadjusted odds ratio [OR] 1.72 [95% CI: 1.06, 2.77], p = 0.027). However, after adjustment for covariates the effect size was smaller and not significant (adjusted OR 1.56 [95% CI: 0.91, 2.68], p = 0.11). There were no differences in stunting at 2 years (Table 2).

WAZ and underweight

Mean WAZ scores were below the WHO standardised median in both groups at 1 and 2 years (Fig. 2; Supplementary Table S5). There were no significant differences in WAZ scores in CHEU compared to CHUU at 1 year (adjusted MD −0.08 [95% CI −0.34, 0.18], p = 0.55), 2 years (adjusted MD −0.06 [95% CI: −0.36, 0.24], p = 0.69) or in mixed linear regression (fully adjusted MD −0.09 [95% CI: −0.33, 0.15] p = 0.48) (Table 2). There were no differences in underweight at 1 year (adjusted OR 1.69 [95% CI: 0.71, 4.03], p = 0.23)

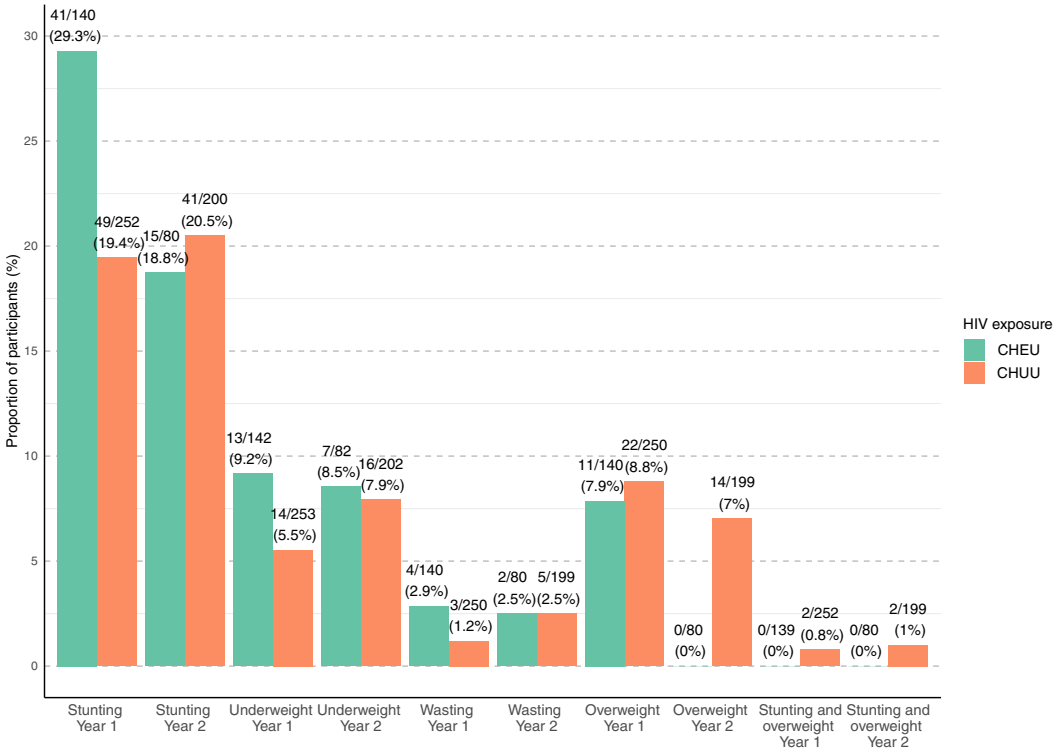

Fig. 3: Stunting, underweight, wasting and overweight in CHEU and CHUU at 1 and 2 years. Prevalence of stunting, underweight, wasting, overweight and combination of stunting and overweight in CHEU and CHUU at 1 and 2 years. Green: CHEU, orange: CHUU. CHEU: children who are HIV-exposed and uninfected; CHUU: children who are HIV-unexposed and uninfected; HIV: human immunodeficiency virus.

or at 2 years (adjusted OR 1.01 [95% CI: 0.34, 2.70], p = 0.98) (Table 2).

WLZ and wasting

Mean WLZ scores were above the WHO standardised median in both groups at 1 year, and close to the median at 2 years (Fig. 2; Supplementary Table S5). There were no significant differences in WLZ scores in CHEU at 1 year (adjusted MD −0.04 [95% CI: −0.31, 0.24], p = 0.80), at 2 years (adjusted MD −0.08 [95% CI: −0.39, 0.23], p = 0.60), or the mixed linear regression (fully adjusted MD −0.06 [95% CI: −0.30, 0.18], p = 0.61) (Table 2). The risk of wasting was higher in CHEU at 1 year (adjusted OR 3.64 [0.62, 31.2], p = 0.17), but not at 2 years (adjusted OR 0.93 [95% CI: 0.11, 5.39], p = 0.94), and neither association was statistically significant (Table 2).

Overweight

The prevalence of overweight was similar in CHEU (7.9%) and CHUU (8.8%) at 1 year (Fig. 3). At 2 years, no CHEU (0%) were overweight compared to 7% of CHUU, resulting in significantly lower odds of being overweight for CHEU, compared to CHUU (adjusted OR 0.12 [95% CI: 0.00, 0.89], p = 0.035) (Table 2). Stunting and overweight co-existed at 1 year in 0/139 (0%) CHEU and 2/252 (0.8%) CHUU, and at 2 years in 0/80 (0%) CHEU and 2/199 (1%) CHUU (Fig. 3). There were no significant differences in the odds of having both stunting and overweight at 1 year (adjusted OR 0.17 [95% CI: 0.00, 9.46]) or at 2 years (adjusted OR 0.52 [95% CI: 0.00, 5.88]) (Table 2).

HCAZ

There were no significant differences in HCAZ scores at 1 year (adjusted MD −0.16 [95% CI: −0.40, 0.07], p = 0.18), 2 years (adjusted MD −0.14 [95% CI: −0.43, 0.14], p = 0.33) or in the mixed linear regression (fully adjusted MD −0.14 [95% CI: −0.36, 0.08], p = 0.23) (Table 2).

Sensitivity analyses

Differential loss to follow up of CHEU and CHUU prompted application of inverse probability weighting to the fully adjusted linear and logistic regression models at year 1 and 2, and to the fully adjusted mixed linear regression models. This analysis showed results that were similar in magnitude and direction to the unweighted models (Supplementary Table S6), suggesting that selection bias due to the characteristics associated with loss to follow-up is unlikely to have materially influenced our findings.

Mediation analyses showed that adding exclusive breastfeeding at discharge from the labour ward, LBW, PTB, SGA or a combined variable of any adverse perinatal outcome to the fully adjusted mixed linear regression model did not substantially affect the association between HIV-exposure and anthropometric Z-scores based on visual inspection of coefficient changes (Supplementary Fig. S2).

The mixed linear regression model restricted to exclusively breastfed children born at term and not SGA, as well as analyses restricted to children who attended both follow-up appointments, and analyses restricted to children with documented evidence of exposure to maternal efavirenz-based ART showed similar results with no significant differences, although there was a consistent, non-significant, trend towards lower Z-scores for CHEU across growth outcomes (Supplementary Table S7).

Finally, there was no interaction between HIV exposure and time, or between HIV exposure and child's sex on any of the growth outcomes in the fully adjusted mixed linear regression model.

Discussion

We found no statistically significant differences in growth in CHEU compared with CHUU up to 2 years, although there was a consistent trend towards slightly delayed growth in CHEU compared to CHUU up to 2 years, with adjusted mean differences of Z-scores between –0.06 and –0.19. The effect sizes observed were small and may be of limited clinical significance. Both groups had mean LAZ and WAZ scores considerably below the WHO standardised median, indicating slower linear growth and lower weight than expected for age. By contrast, WLZ scores were above the standardised median at year 1, then closer to the standardised median at year 2. The prevalence of stunting was high in both groups at both timepoints. At 1 year, CHEU had significantly higher odds of stunting in unadjusted analyses only, while at 2 years there was no difference in stunting between the two groups. While the risk of overweight was similar between the groups at 1 year, CHEU had significantly lower odds of being overweight at 2 years.

Our findings are consistent with previous studies conducted in similar socioeconomic settings that found slightly delayed growth in CHEU exposed to ART during pregnancy, compared to CHUU.[6,9,26] One cohort study in South Africa found consistently lower WAZ and WLZ scores in breastfed CHEU who were also exposed to maternal ART, compared to CHUU, during 3-monthly visits from birth until 12 months, and lower LAZ scores in CHEU from 6 to 12 months.[6]

Stunting prevalence was similar to the estimated national prevalence of stunting in children under 5 years (21.2%) in South Africa in 2015.[27] We found a higher risk of stunting in CHEU at 1 year in unadjusted analyses, however, after adjusting for potential confounders, this association was no longer significant. This may be explained by confounding due to baseline differences between groups in maternal and household characteristics, including maternal age, education, socioeconomic status and nulliparity, which are established predictors of growth. Several other studies have found a higher risk of stunting in CHEU who were also exposed to maternal ART, compared to CHUU.[6,9,26,28–30] Although children who are SGA are known to have a higher risk of linear growth faltering,[31] adjusting for SGA in our sensitivity analyses did not affect the relationship between HIV exposure and LAZ scores.

We found no difference in the risk of underweight between CHEU and CHUU. Previous studies show disparate findings on the risk of underweight in CHEU who were also exposed to maternal ART, compared to CHUU, with some finding a higher risk of underweight in CHEU,[6,9,14] while others found no difference.[29]

Our finding that there was no difference in wasting between CHEU and CHUU aligns with findings from other studies under conditions of a recommendation of ART for all people living with HIV.[6,28,29]

One cohort study of CHEU and CHUU in South Africa, found that nearly 20% of participants were overweight by 1 year,[6] compared to 8.5% of all participants at 1 year in our study. Notably, in our study, at year 2 CHEU had significantly lower odds of being overweight, compared to CHUU. Reassuringly, we found a low prevalence of children who had both stunting and overweight.

Most studies assessing growth in CHEU have been small and may be underpowered to detect modest but potentially important differences in growth outcomes. Reported data on maternal HIV disease severity and ART are often limited. A systematic review and meta-analysis of studies that consistently report maternal ART would help further clarify any potential differences in growth outcomes between CHEU and CHUU.

The mechanisms underlying slightly slower growth in CHEU across anthropometric Z-scores are likely multifactorial. Foetal immune activation in response to a pro-inflammatory environment in utero may delay intrauterine growth, in turn predisposing to stunting and wasting, though notably our study found no differences in SGA at birth between CHEU and CHUU.[3] HIV-affected households, and thereby CHEU, are also more likely to experience socioeconomic deprivation and food insecurity,[32,33] which are strong determinants of impaired childhood growth.[34] However, in our study, adjustment for socioeconomic status did not materially change the association between HIV-exposure and growth. Differences in breastfeeding practices may also influence growth in CHEU. Breastfeeding promotes

healthy growth through providing adequate infant nutrition and preventing childhood infections that otherwise could delay growth.[35] In our study CHEU had a lower rate of exclusive breastfeeding, but our mediation analysis showed no effect of adjusting for exclusive breastfeeding in the association between CHEU and growth Z-scores. However, it is important to note that this sensitivity analysis was based on breastfeeding at discharge from the labour ward, since we did not have access to data on duration of exclusive breastfeeding. Although WHO recommends that all children are exclusively breastfed for at least 6 months, a recommendation that includes mothers living with HIV who are well controlled on ART, early cessation of breastfeeding may be more likely in CHEU and could account for some of our findings.

This study was conducted in a well characterised cohort of participants recruited during early foetal life and followed up until 2 years postpartum, enabling for adjustment of key covariates. However, the data were obtained from a single urban site in South Africa and during the era of efavirenz-based ART as the first-line regimen, so the generalisability to other socioeconomic and geographic settings, and to current dolutegravir-based ART regimens, may be limited.

This cohort study has several strengths. First, data were collected prospectively by trained research staff from children whose mothers were recruited during the first trimester of pregnancy and followed up closely until delivery, with standardised measures including accurate ultrasound-based first trimester gestational age estimation and birthweight assessment at birth. Detailed data were also collected on socioeconomic status, maternal medical and obstetric history, and perinatal outcomes. Second, anthropometric measures were recorded in duplicate in a highly standardised manner during each study visit, which allowed for consistency checks.

The study had some important limitations. First, data on antenatal ART exposure were only available for 46% of CHEU; however, it is likely that most CHEU were exposed to antenatal ART. South African guidelines at the time of study conduct recommended universal HIV testing at first antenatal appointment and treatment for all people living with HIV with efavirenz-based ART as first-line, and the national coverage of antenatal ART for prevention of mother-to-child transmission at the time (2014) was 98%.[36] There was no recorded mother-to-child HIV transmission at birth in this cohort, which implies good ART coverage, and subgroup analyses restricted to children known to be exposed to efavirenz-based ART showed similar results to the overall analysis. Second, data on maternal HIV disease severity (CD4 count and viral load) were not available. Third, no data were available on infant post-exposure prophylaxis or co-trimoxazole prophylaxis. South African guidelines at the time recommended infant post-exposure prophylaxis with nevirapine at birth and then daily for 6 weeks, and co-trimoxazole prophylaxis from 4 to 6 weeks after birth until 6 weeks after cessation of breastfeeding and confirmation using polymerase chain reaction test that the child was not living with HIV.[17,37] Fourth, the longitudinal data on breastfeeding at 1 and 2 years did not allow us to accurately estimate the duration of exclusive breastfeeding during the first 6 months. Therefore, data on exclusive breastfeeding were only available at discharge from hospital, and not during follow-up appointments. Since breastfeeding affects early child growth, the absence of data on duration of exclusive breastfeeding may have introduced residual confounding. Fifth, the sample size was relatively small and may not have been sufficiently powered to detect smaller differences in growth between exposure groups. For most outcomes, the mean differences between groups were smaller than the minimum detectable mean differences with 80% power, suggesting that the study was underpowered to detect the small effect sizes observed. A larger study would have had higher power to detect such relatively small differences. Finally, there was considerable loss to follow-up, with a higher proportion of CHEU lost to follow-up. Some key characteristics, such as maternal education, socioeconomic status and perinatal outcomes, which are associated with child growth differed between participants that were retained and lost to follow-up. Thus, due to attrition, the composition of the two exposure groups differed between the year 1 and year 2 visits, which may have introduced selection bias. However, sensitivity analyses using inverse probability weighting models produced results that were consistent with the primary models in magnitude and direction, suggesting that selection bias due to attrition is unlikely to have materially influenced the findings. Additionally, analyses restricted to participants with data at both follow-up appointments yielded similar results.

In conclusion, we report marginally lower growth Z-scores, most of which are not statistically significant, in CHEU in the era of universal ART, compared to CHUU. Stunting was common in both CHEU and CHUU, and CHEU had higher risk of stunting at 1 year in unadjusted analyses. Risk of overweight was similar in the two groups at 1 year, but CHEU had significantly lower risk of being overweight at 2 years. Stunting is a marker of chronic undernutrition and childhood illness, which may impair cognition and predispose to chronic disease in adulthood. Therefore, it is crucial to identify children more at risk of growth impairment, such as CHEU, and identifying the specific mechanisms causing stunting in this population, to enable development of targeted interventions that optimise growth in this population. Future, well powered, prospective studies may further assess these associations in the context of the current first-line dolutegravir-based ART regimen.

Contributors
AC, MQ and JH conceived of the present study. AC cleaned and analysed the data, developed the figures and tables, interpreted the data and wrote the manuscript, all with inputs from MQ and JH. MQ and JH have access to and verify the underlying study data. SN was primarily responsible for data collection for the original study in South Africa, which was conceived, designed and implemented by the INTERBIO-21st Consortium.

Data sharing statement
Data sharing: study data are available with publication on reasonable request to the INTERBIO-21st Consortium. No restrictions are applied a priori.

Declaration of interests
JH declares membership of the writing group of the British HIV Association guidelines on the management of HIV in pregnancy and the postpartum period 2025. The other authors declare no conflicts of interest.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103515.

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