Growth patterns of infants with \textit{in-} utero HIV and ARV exposure in Cape Town, South Africa and Lusaka, Zambia

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Abstract

**Background:** Infants born HIV-exposed yet remain uninfected (HEU) are at increased risk of poorer growth and health compared to infants born HIV-unexposed (HU). Whether maternal antiretroviral treatment (ART) in pregnancy ameliorates this risk of poorer growth is not well understood. Furthermore, whether risks are similar across high burden HIV settings has not been extensively explored.

**Methods:** We harmonized data from two prospective observational studies conducted in Cape Town, South Africa, and Lusaka, Zambia, to compare weight-for-age (WAZ), length-for-age (LAZ) and weight-for-length (WLZ) Z-scores between infants who were HEU and HU, converting infant anthropometric measures using World Health Organisation Growth Standards adjusted for age and sex. Linear mixed effects models were fit to identify risk factors for differences in anthropometrics at 6–10 weeks and 6 months by infant HIV exposures status and by timing of exposure to maternal ART, either from conception or later in gestation.

**Results:** Overall 773 mother-infant pairs were included across two countries: women living with HIV (WLHIV), 51% (\(n = 395\)) with 65% on ART at conception and 35% initiating treatment in pregnancy. In linear mixed effects models, WAZ and WLZ at 6–10 weeks were lower among infants who were HEU vs HU \([\beta = -0.29 (95\% CI: -0.46, -0.12)]\) and \([\beta = -0.42 (95\% CI: -0.68, -0.16)]\) respectively after adjusting for maternal characteristics and infant feeding with a random intercept for country. At 6 months, LAZ was lower \([\beta = -0.28 CI: -0.50, -0.06)]\) among infants who were HEU, adjusting for the same variables, with no differences in WAZ and WLZ. Within cohort evaluations identified different results with higher LAZ among infants who were HEU from Zambia at 6–10 weeks, \([\beta = +0.34 CI: +0.01, +0.68)]\) and lower LAZ among infants who were HEU from South Africa \([\beta = -0.30 CI: -0.59, -0.01)]\) at 6 months, without other anthropometric differences at either site.

**Conclusion:** Infant growth trajectories differed by country, highlighting the importance of studying contextual influences on outcomes of infants who were HEU.

**Keywords:** HIV-exposed uninfected, HIV-unexposed, antiretroviral therapy, weight-for-age, length-for-age, South Africa, Zambia

Introduction

Scale-up of maternal antiretroviral treatment (ART) use in pregnancy to prevent vertical HIV transmission has been one of the most successful global public health initiatives. However, the impact of maternal ART on growth and development of HIV-exposed uninfected (HEU) infants remains unclear, especially in high-burden settings. This study aimed to compare the growth patterns of HEU and HIV-unexposed (HU) infants in Cape Town, South Africa, and Lusaka, Zambia, with a focus on the role of maternal ART in pregnancy.
health programs. As a result, an unprecedented num-
ber of women are taking ART at conception and during
pregnancy with over 1 million women living with HIV
(WLHIV) giving birth annually [1]. This success has dra-
matically reduced the number of infants who acquire
HIV, contributing to a large and growing population of
infants with in-utero dual exposure to HIV and antiretro-

while vertical HIV transmission prevention programs
have improved the health of women living with HIV
and averted infant HIV acquisition, infants who are HIV
exposed but uninfected (HEU) experience a higher risk
of poor health outcomes compared to infants who are
HIV-unexposed (HU). Whether poorer outcomes are
due to in-utero exposure to HIV or ARVs, poor mater-

al health, increased presence of infectious pathogens in
households affected by HIV, or poverty related factors
often present in households affected by HIV, including
food insecurity, has yet to be clearly delineated. Several
studies have reported that infants who are HEU experi-
ence poorer growth, health and survival outcomes com-
pared to infants who are HU, starting from birth [2–9].
This has brought into question the extent to which fetal
exposure to ARVs and the duration of exposure, either
from conception or at a later period of gestation, may
be contributing to this disparity. Also, infants born HEU
have increased risk of infectious morbidity and mortal-
ity when compared to infants born HU [10, 11]. While
the causes of this increased morbidity in infants who are
HEU are multifactorial, in-utero exposure to ARVs may
be a contributing factor. Recent studies have shown reas-
uring results that breastfeeding while on ART is the
optimal feeding strategy for HIV-exposed infants in most
resource-limited settings [5, 12, 13]. However, it is cause
for concern that the comparative growth of infants who
are HEU and HU has highlighted early onset of obesity
in late infancy [5]. As the HIV epidemic has matured,
with programs to prevent vertical transmission of HIV
through universal ART for pregnant women, (World
Health Organization Option B) and continuation of this
ART for life (World Health Organization Option B+), the
types of ART recommended for use in pregnancy, as well
as the proportion of women on ART prior to concep-
tion have evolved. Given few randomized studies evalu-
ating the safety of different ART regimens in pregnancy,
and the absence of equipoise to conduct such trials now,
ongoing drug safety surveillance is critical. Identifying
the safest ART regimens that optimize maternal and
child outcomes represents a key public health challenge.
Locations with generalized HIV epidemics and high dis-

ease burden are best positioned to provide answers.

South Africa’s antenatal HIV prevalence is one of
the highest globally, reported as approximately 30% in
2017 [14]. Zambia’s antenatal HIV prevalence has been
reported as 13.3% nationally but as high as 30% in Lusaka
[15]. In these high prevalence settings, more than 95% of
pregnant WLHIV receive ART in pregnancy, resulting in
the majority of infants who are HEU having dual expo-
sure to HIV and ARVs. While not all studies show the
same early adverse outcomes of in-utero exposures, some
have found alterations in growth [8, 9, 16–20]. In particu-
lar, infants who are HEU may experience a higher risk of
suboptimal growth in infancy [4, 5, 8, 13, 16–18, 20–22]
with these effects persisting through to school-going age
[7, 23]. Many studies however, (1) lack comparison with
children who are HU. This limits the ability to differen-
tiate between the effects of fetal HIV and ARV exposure
from effects of the socio-economic environment and
health interventions, precluding an understanding of the
extent to which biological, socio-economic, or structural
factors might be contributing to poor growth among
infants who are HEU. (2) Additionally, much of the pub-
ished research in this area reflects outcomes during the
early period of implementation of WHO Option B+ (life-
long triple ART for pregnant and breastfeeding women).
As such, there are fewer data on infant growth following
ARV exposure from conception and on health outcomes
of infants who are HEU in the context of widespread
breastfeeding up to 24 months. (3) Furthermore, some
of the studies reporting absence of growth differences
between infants who are HEU, and HU may not have
been adequately powered to detect small but clinically
important differences [5, 24, 25]. Pooling of data between
studies has not been routinely performed to achieve ade-
quate statistical power to detect these potentially small
but clinically meaningful differences. To evaluate the
effect of ARV exposure specifically, timing and duration
of fetal exposure must be studied among children born
to WLHIV. We pooled prospectively collected data from
the B-Positive cohort conducted in Cape Town, South
Africa, and the B+Readiness cohort in Lusaka, Zambia
to evaluate associations between in-utero exposure to
HIV/ maternal ART and infant anthropometrics by HIV
and maternal ART exposure status, controlling for socio-

economic differences.

Methods
Study setting
We collated data from two observational prospective
studies enrolling pregnant women attending antenatal
care (ANC) at primary maternity care facilities in Cape
Town, South Africa and Lusaka, Zambia. Mother-infant
pairs were followed from the child’s birth to at least
6 months of life. The study in Cape Town (B-Positive
study) was conducted at a large primary healthcare facil-
ity in Gugulethu, an urban township in Cape Town. The
facility serves a population of about 350,000 with an estimated antenatal HIV prevalence of 30% in 2015 [26]. The study in Lusaka (B+ Readiness) was a conducted by the Centre of Infectious Disease Research Zambia (CIDRZ) in Lusaka. The antenatal HIV prevalence in Lusaka was estimated to be 30% in 2014 [15]. Both studies were prospective observational studies.

**Study design and study participants**

Consecutive pregnant women ≥18 years of age were recruited at their first ANC visit, at both study sites, regardless of HIV status. Study enrolment in both sites occurred between January 2017 and October 2018. In both sites, women were eligible for this study if they planned to reside in the area with their infants until infants were 6 months old and had a known maternal HIV status. Maternal HIV-positivity was based on clinic records and HIV-negative was based on a negative HIV-1/2 rapid antibody test at cohort enrolment.

**Study procedures**

All eligible pregnant women who provided informed written consent were enrolled. Birth anthropometrics were abstracted from the child Road to Health Booklets (RTHB) in South Africa and the Under-5 health booklet in Zambia. Birth weight of newborns was measured within 24 h of birth by health facility nurses. Mother-infant pairs were evaluated by the study teams postnatally between 6 and 10 weeks and at 6 months of life. To be included in this secondary analysis, a woman had to deliver a liveborn, singleton infant, birth weight and/or length data had to be available in the child’s RTHB/Under-5 booklet and have infant anthropometric measurements recorded at either 6–10 weeks and 6 months of life.

**Data collection**

Data collected included maternal demographics, pregnancy history, healthcare information, delivery/birth details, child health encounters and feeding practices. Identical standardized questionnaires were administered to all women by trained study interviewers at both study sites. Pregnant women with a negative HIV test at enrolment based on routine rapid antibody test were retested immediately after delivery or during the newborn visit occurring within 3–7 days after delivery, and approximately every 3 months during breastfeeding, as per South African [27] and Zambian standard guidelines [28]. HIV DNA PCR testing of infants occurred at birth, and 6 to 10 weeks in South Africa and at 6 weeks and 6 months in Zambia, per national guidelines. Maternal HIV history and other medical conditions were based on medical records. Per study protocol, during the 6–10 week and 6-month study visits infants were weighed using a calibrated digital infant scale by trained study staff after removal of clothing and diapers. All infant length measurements were taken while the infant was recumbent using an infant length measuring board. Two measurements of infant weight and recumbent length were taken at each visit by study staff and the average was calculated. The study clinician conducted regular anthropometric training for all study staff with structured, supervised and competency assessments. Research Electronic Data Capture (REDCap), a secure, web-based application designed to support data capture for research studies, was employed at both study sites to capture study data and University of Cape Town served as the data centre for the pooled, harmonized data [29]. Sample size calculations were done for independent cohort studies to provide good statistical power to examine associations with maternal and infant factors likely to affect HEU infant growth, adequately adjusting for multiple confounders. We had a unique opportunity to use data from the two studies, allowing for sufficient power to identify any difference in the growth of infants who were HEU compared to HU.

**Exposures and Outcomes**

For this analysis, we used data collected during the 6–10 week and 6 month study visits. We evaluated two primary exposures of interest. The first was fetal exposure to HIV, while the second focused on timing of ARV exposure and only included infants who were HEU. A dichotomous variable of either ARV exposure from conception versus later in gestation was derived from maternal ART data. The outcomes of interest were infant weight-for-age (WAZ), length-for-age (LAZ) and weight-for-length (WLZ) z-scores, converted from measured weight and length using the WHO Growth Standards, which adjust for infant age in days and infant sex [30]. Child age at each time point was derived using the visit date and the child’s date of birth. As per WHO guidelines, z-scores out of the range of −3 and +3 from the median for the reference population were reviewed and corrected in the event of data capturing errors. Unexplained z-scores out of the range of −5 and +5 from the median for the reference population were excluded from the analysis [~2% observations were omitted in the analysis (n = 16)]. We used the WHO guidelines to define underweight as WAZ of less than −2 standard deviations and stunting as LAZ of less than −2 standard deviations from the median reference population [30].

**Statistical analysis**

Data were analysed using Stata 14.0 (Stata Corporation, College Station, TX, USA) [31]. Maternal and infant
characteristics were compared using Wilcoxon rank-sum test and χ² test as appropriate. We presented comparison of maternal and infant characteristics stratified by country in supplementary material. Proportions of secondary outcomes, specifically infants underweight or stunted, were compared by an infant’s in-utero HIV exposure status and, only among infants who were HEU, by timing of in-utero ARV exposure, from conception vs later in gestation. Univariable and multivariable linear mixed models were fit to compare the primary outcomes, mean WAZ, LAZ and WLZ scores first by in-utero HIV exposure status, then for infants who were HEU, by timing of in-utero ARV exposure. The linear mixed effects models were fitted separately for WAZ, LAZ and WLZ including random effects for intercept and an unstructured correlated covariance matrix was assumed for random effects. All covariates in univariable analyses with a p-value of 0.10 were included in multivariable analyses. Additionally, an a priori decision was made to include maternal age in the multivariable model, regardless of univariable p-value [3, 32, 33]. Infant feeding practice was defined as exclusive breastfeeding, formula feeding, or mixed feeding based on maternal report. We performed a sensitivity analysis by restricting our analysis to infants who had similar feeding patterns, that is infants who had exclusive breastfeeding up to 6 months of life.

**Ethical considerations**

This study was approved by the University of Cape Town’s Faculty of Health Sciences Research Ethics Committee (UCT-HREC-514/2015 and 749/2015), the Western Cape Government Department of Provincial Health Research Committee (WC-2016RP6_286) and University of Zambia Biomedical Research Ethics Committee (UNZA-REC – 007-12-17). All women participating in the study provided informed written consent for their own participation and that of their child’s.

**Results**

A total of 1032 pregnant women were enrolled in the B Positive cohort in Cape Town and the B+ Readiness cohort in Lusaka, 773 mother-infant pairs with live singleton births were included in this analysis. Mother-infant pairs excluded from this analysis have reasons listed in (Fig. 1). Of the 773 infants, 395 (51%) were HEU, while 378 (49%) were HU. Maternal and infant characteristics are shown in Table 1. Women living with HIV were older (median age = 32 years; IQR 28–33) versus 378 (49%) were HU by 6 to 10 weeks of age, and 6% (n = 24) of 395 infants who were HEU had low birthweight, compared with 5% (n = 22) of 378 infants who were HU (p = 0.88). A significant lower proportion of infants who were HEU exclusively breastfed for a full 6 months compared to infant who were HU (32% versus 45%, p < 0.001). Complementary feeding (solid food or nutritive liquids other than breastmilk or formula milk) had been introduced to 6% (n = 24) of 395 infants who were HEU versus 14% (n = 51) of the 373 infants who were HU by 6 to 10weeks of age, and 6% (n = 24) of 395 versus 15% (n = 58) of 373 by 6 months of age (Table 1). A greater proportion of infants who were HEU switched from exclusive breastfeeding to exclusive formula feeding by 6 months of age (Table 1). Characteristics of infants who are HEU only stratified by timing of maternal ART initiation did not show any difference (Table 2). Characteristics of infants stratified by country showed some differences shown in supplementary material (Table S1). At 6 months of life, female infants who were HEU had significantly lower weight compared to female infants who were HU in the South Africa cohort, but this was not the same in the Zambia cohort. In South Africa cohort, infants who were HEU had significantly lower LAZ with mean LAZ − 0.79 versus − 0.45 (p-value =0.008) in infants who were HU, but this was not the case in the
At 6 months of life, there was a difference in infant feeding practices in South Africa cohort between infants who were HEU compared to HU (p-value < 0.001) but there was no difference in Zambia cohort (p-value = 0.23). The growth pattern of infants by country is shown in Fig. 2.

In the pooled data between South Africa and Zambia, infants who were HEU were more likely to be underweight at 6 to 10 weeks of life, 7.8% (31 of 395 infants) compared to 3.2% (12 of 378) of infants who were HU (Fig. 3). This difference was less pronounced at 6 months, with 4.6% for infants who were HEU being underweight compared to 2.6% of children who were HU. There was no association between underweight and infant feeding practices at either 6 to 10 weeks or 6 months of age (p = 0.39 and p = 0.69, respectively).

In linear mixed effects models of pooled results from both cohorts, WAZ and WLZ at 6 to 10 weeks were lower among infants who were HEU compared to those who were HU ($\beta = -0.29$ (95% CI: $-0.46, -0.12$) and $\beta = -0.42$ (95% CI: $-0.68, -0.15$)) after adjusting for maternal age, maternal BMI, infant feeding practice,
Table 1  Characteristics of women and infants by HIV status at 6/10 weeks and 6 months in Cape Town, South Africa and Lusaka, Zambia

| Maternal characteristics | Total (n, %) | Women living without HIV (378, 49) | Women living with HIV (395, 51) | P-value |
|--------------------------|-------------|------------------------------------|---------------------------------|---------|
| **Sociodemographic**     |             |                                    |                                 |         |
| Age (median, IQR) years  | 29 (25–34)  | 27 (23–32)                         | 31 (26–35)                      | <0.001  |
| Weight at 6/10 weeks (median, IQR) kg | 68 (59–83) | 69 (60–87)                        | 67 (57–80)                      | 0.01    |
| Weight at 6 mons (median, IQR) kg | 69 (58–85) | 71 (60–89)                        | 66 (56–81)                      | 0.001   |
| Height (median, IQR) metres | 1.58 (1.54–1.63) | 1.58 (1.54–1.62) | 1.59 (1.55–1.63) | 0.03    |
| Maternal BMI at 6/10 weeks (kg/m²) | 27 (24–33) | 28 (25–34)                        | 27 (23–31)                      | <0.001  |
| Maternal BMI at 6 months (kg/m²) | 27 (24–33) | 29 (24–35)                        | 26 (23–32)                      | <0.001  |
| **ART initiation**       |             |                                    |                                 |         |
| Receiving ARVs at conception | 256 (65) * | –                                  | 256 (65)                        |         |
| Resuming/initiating ARVs during pregnancy | 139 (35) * | –                                  | 139 (35)                        |         |
| **ART duration in pregnancy (median, IQR) weeks** | 37 (24–39) | 37 (24–39)                        | 37 (24–39)                      |         |
| **Education level completed** |             |                                    |                                 | <0.001  |
| Primary                  | 111 (14)    | 33 (9)                             | 78 (20)                         |         |
| Secondary                | 636 (82)    | 330 (87)                           | 306 (77)                        |         |
| Tertiary (University)    | 26 (4)      | 15 (4)                             | 11 (3)                          |         |
| **Relationship with father of child** |             |                                    |                                 | 0.42    |
| Married/Cohabiting       | 486 (63)    | 243 (64)                           | 243 (62)                        |         |
| Not married/Non-cohabiting | 287 (37)   | 135 (36)                           | 152 (38)                        |         |
| **Employment status**    |             |                                    |                                 | 0.21    |
| Formal employment        | 187 (24)    | 81 (21)                            | 106 (27)                        |         |
| Informal employment      | 45 (6)      | 26 (6)                             | 22 (6)                          |         |
| Unemployed/attending school | 541 (70)  | 274 (72)                           | 267 (67)                        |         |
| **Child characteristics** |             |                                    |                                 |         |
| Sex                      |             |                                    |                                 |         |
| Male                     | 379 (49)    | 189 (50)                           | 190 (48)                        | 0.59    |
| Female                   | 394 (51)    | 189 (50)                           | 205 (52)                        |         |
| Age at 6/10 weeks (median, IQR) in days | 70 (51–73) | 70 (57–74)                        | 69 (49–73)                      | 0.06    |
| Age at 6 months (median, IQR) in days | 184 (181–193) | 183 (180–191) | 184 (181–196) | 0.04    |
| Weight at birth (median, IQR) kg |             |                                    |                                 |         |
| Male                     | 3.1 (2.9–3.5) | 3.2 (2.9–3.5) | 3.1 (2.8–3.5) | 0.24    |
| Female                   | 3.1 (2.8–3.4) | 3.2 (2.9–3.5) | 3.1 (2.8–3.3) | <0.001  |
| Low weight at birth (< 2.5 kg) |             |                                    |                                 |         |
| Male                     | 25 (7)      | 15 (8)                             | 10 (5)                          | 0.29    |
| Female                   | 21 (5)      | 7 (4)                              | 14 (7)                          | 0.17    |
| Weight at 6/10 weeks (median, IQR) kg |             |                                    |                                 |         |
| Male                     | 5.5 (4.8–6.2) | 5.8 (5.1–6.4) | 5.3 (4.7–5.9) | <0.001  |
| Female                   | 5.2 (4.6–5.8) | 5.3 (4.8–6.0) | 5.0 (4.5–5.7) | 0.001   |
| Weight at 6 months (median, IQR) kg |             |                                    |                                 |         |
| Male                     | 7.8 (7.1–8.7) | 7.9 (7.2–8.8) | 7.6 (7.0–8.6) | 0.16    |
| Female                   | 7.3 (6.7–8.2) | 7.5 (6.8–8.5) | 7.2 (6.7–8.0) | 0.03    |
| Length at 6/10 weeks (median, IQR) cm |             |                                    |                                 | 0.14    |
| Male                     | 57 (53–59)  | 57 (53–60)                         | 56 (54–58)                      |         |
| Female                   | 56 (53–58)  | 56 (53–58)                         | 56 (53–58)                      | 0.39    |
| Length at 6 months (median, IQR) cm |             |                                    |                                 | 0.002   |
| Male                     | 66 (63–68)  | 66 (63–69)                         | 65 (63–67)                      |         |
| Female                   | 64 (62–67)  | 64 (62–67)                         | 64 (62–66)                      | 0.34    |
| **Z-scores at 6/10 weeks, mean (SD)** |             |                                    |                                 |         |


marital and employment status and country (Table 3). When evaluated by country at 6–10 weeks’ time point, WAZ was lower among infants who were HEU compared to those who were HU at both the South Africa and Zambia country \( [\beta = -0.23 (95\% \text{ CI}: -0.47, -0.01)] \) and \( [\beta = -0.31 (95\% \text{ CI}: -0.59, -0.04)] \), respectively. At 6–10 weeks, there were no differences for LAZ and WLZ by HIV exposure status in the South Africa cohort, while LAZ was higher \( [\beta + 0.34 (95\% \text{ CI}: 0.01, 0.68)] \) and WLZ was lower \( [\beta = -0.092 (95\% \text{ CI}: -1.39, -0.44)] \) for infants who were HEU compared to those who were HU in the Zambia cohort. At 6 months, LAZ was lower \( [\beta = -0.28 (95\% \text{ CI}: -0.50, -0.06)] \) in the data pooled between the two countries, after adjusting for the same covariates. Evaluation by each cohort individually revealed no differences at 6 months in WAZ and WLZ by group. However, in the South Africa cohort, infants who were HEU had lower LAZ compared to those who were HU in adjusted analyses \( [\beta = -0.30 (95\% \text{ CI}: -0.59, -0.01)] \). In Zambia cohort, infants who were HEU had lower LAZ but not significantly different compared to those who were HU in adjusted analyses \( [\beta = -0.22 (95\% \text{ CI}: -0.58, +0.14)] \).

Evaluation of fetal timing of ARV exposure, either from conception or later during gestation did not identify any differences in WAZ, LAZ and WLZ at 6–10 weeks or 6 months among infants who were HEU (Table 4). In a sensitivity analysis, by limiting the analysis to infants who had exclusive breastfeeding up to 6 months, WAZ for pooled data at 6 to 10 weeks was lower among infants who were HEU compared to those who were HU \( [\beta = -0.29 (95\% \text{ CI}: -0.58 -0.01)] \) but was resolved 6 months \( [\beta = +0.02 (95\% \text{ CI}: -0.28 + 0.32)] \) (Table S2). When evaluated within cohorts, LAZ was significantly higher among infants who were HEU compared to those who were HU in Zambia cohort \( [\beta = +0.61 (95\% \text{ CI}: +0.09 +1.13)] \) while the results from South Africa cohort were in a different direction \( [\beta = -0.41 (95\% \text{ CI}: -0.85 + 0.02)] \). All the differences were resolved by 6 months.

**Discussion**

In this prospective cohort of pregnant women seeking ANC at peri-urban public health care facilities in South Africa and Zambia, we found that infants who were HEU experienced lower mean WAZ and WLZ at 6 to 10 weeks of age compared to infants who were HU. However, these differences were no longer present by 6 months of life. In contrast, we found that infants who were HEU experienced lower mean LAZ at 6 months of age compared to those who were HU, despite the fact that LAZ was similar between these two groups at 6 to 10 weeks of life. In evaluating timing of ARV exposure for infants who were HEU, mean WAZ, LAZ and WLZ did not vary between those infants with foetal exposure from time of conception and those exposed later in gestation.

Our finding of lower WAZ at 6 to 10 weeks among infants who were HEU is consistent with several studies in African populations \([2, 5, 9, 19]\). It was reassuring that HEU appeared to catch-up in terms of WAZ by 6 months. On the other hand, rapid catch-up growth in infancy may have negative consequences, including a future risk of obesity and cardiovascular disease in adulthood \([5, 7]\).
## Table 2  Characteristics of women living with HIV and their infants by timing of maternal ART initiation at 6/10 weeks and 6 months in Cape Town, South Africa and Lusaka, Zambia

| Maternal Characteristics | Total (n, %) | Women who start ART during pregnancy | Women on ART at conception | P-value |
|--------------------------|-------------|--------------------------------------|---------------------------|---------|
|                          | 395         | 139 (35)                             | 256 (65)                  |         |
| **Sociodemographic**     |             |                                      |                           |         |
| Age (median, IQR) years  | 31 (26–35)  | 28 (25–33)                           | 32 (28–36)                | <0.001  |
| Weight at 6/10 weeks (median, IQR) kg | 67 (57–80) | 65 (57–76)                           | 68 (57–82)                | 0.21    |
| Weight at 6 months (median, IQR) kg | 66 (55–81) | 64 (55–78)                           | 68 (58–84)                | 0.05    |
| Height (median, IQR) metres | 1.59 (1.55–1.63) | 1.58 (1.54–1.62) | 1.59 (1.55–1.63) | 0.07    |
| Maternal BMI at 6/10 weeks (kg/m2) | 27 (23–31) | 26 (23–31)                           | 27 (23–32)                | 0.40    |
| Maternal BMI at 6 months (kg/m2) | 26 (23–32) | 25 (23–32)                           | 27 (23–33)                | 0.12    |
| **ART regimen**          |             |                                      |                           |         |
| TDF‑XTC‑EFV              | 318 (80)    | 119 (86)                             | 199 (77)                  | 0.08    |
| Other regimens           | 77 (17) *   | 20 (14)                              | 57 (20)                   |         |
| **ART duration in pregnancy (median, IQR) weeks** | 37 (24–39) | 19 (14–25)                           | 38 (37–39)                |         |
| **Education level completed** |           |                                      |                           |         |
| Primary                  | 78 (20)     | 29 (21)                              | 49 (19)                   | 0.34    |
| Secondary                | 306 (77)    | 104 (75)                             | 202 (79)                  |         |
| Tertiary (University)    | 26 (411 (3))| 6 (4)                                | 5 (2)                     |         |
| **Relationship with father of child** |       |                                      |                           |         |
| Married/Cohabiting       | 243 (62)    | 90 (65)                              | 153 (60)                  | 0.33    |
| Not married/ non-cohabiting | 152 (38)  | 49 (35)                              | 103 (40)                  |         |
| **Employment status**    |             |                                      |                           |         |
| Formal employment        | 106 (27)    | 31 (22)                              | 75 (29)                   | 0.23    |
| Informal employment      | 22 (6)      | 10 (7)                               | 12 (5)                    |         |
| Unemployed/attending school | 267 (67) | 98 (70)                              | 169 (66)                  |         |
| **Child characteristics**|             |                                      |                           |         |
| Child sex                |             |                                      |                           |         |
| Male                     | 190 (48)    | 65 (47)                              | 125 (49)                  | 0.69    |
| Female                   | 205 (52)    | 74 (53)                              | 131 (51)                  |         |
| Age at 6/10 weeks (median, IQR) in days | 69 (49–73) | 68 (47–73)                           | 70 (50–73)                | 0.23    |
| Age at 6 months (median, IQR) in weeks | 26 (26–28) | 26 (26–28)                           | 26 (26–28)                | 0.15    |
| Infant weight at birth (median, IQR) kg |           |                                       |                           |         |
| Male                     | 3.1 (2.8–3.5) | 3.2 (2.8–3.5)   | 3.1 (2.9–3.4)            | 0.44    |
| Female                   | 3.1 (2.8–3.3) | 3.1 (2.8–3.3)   | 3.0 (2.8–3.3)            | 0.64    |
| Weight at 6/10 weeks (median, IQR) kg |           |                                       |                           |         |
| Male                     | 5.3 (4.7–5.9) | 5.2 (4.6–5.6) | 5.5 (4.7–6.0)             | 0.04    |
| Female                   | 5.0 (4.5–5.7) | 5.1 (4.6–5.7) | 5.0 (4.4–5.6)             | 0.54    |
| Weight at 6 months (median, IQR) kg |           |                                       |                           |         |
| Male                     | 7.6 (7.0–8.6) | 7.5 (7.0–8.2) | 7.8 (7.1–8.7)             | 0.11    |
| Female                   | 7.2 (6.7–8.0) | 7.4 (6.9–8.0) | 7.2 (6.6–8.0)             | 0.25    |
| Length at 6/10 weeks (median, IQR) cm |           |                                       |                           |         |
| Male                     | 56 (54–58) | 55 (53–58)                           | 57 (54–58)                | 0.28    |
| Female                   | 56 (53–58) | 55 (53–58)                           | 56 (53–58)                | 0.63    |
| Infant length at 6 months (median, IQR) cm |           |                                       |                           |         |
| Male                     | 65 (63–67) | 65 (63–67)                           | 65 (63–67)                | 0.66    |
| Female                   | 64 (62–66) | 64 (61–66)                           | 64 (62–66)                | 0.36    |
| **Z-scores at 6/10 weeks, mean (SD)** |       |                                       |                           |         |
| Weight-for-age           | −0.34 (1.14) | −0.35 (1.13) | −0.34 (1.15)             | 0.92    |
| Length-for-age           | −1.12 (1.37) | −1.04 (1.46) | −1.16 (1.32)             | 0.37    |
| Weight-for-length        | 0.96 (1.75) | 0.87 (1.86)                           | 1.01 (1.69)               | 0.43    |
Table 2 (continued)

| Maternal Characteristics | Total (n, %) | Women who start ART during pregnancy | Women on ART at conception | P-value |
|--------------------------|-------------|-------------------------------------|-----------------------------|--------|
|                          | 395         | 139 (35)                            | 256 (65)                    |        |
| Z-scores at 6 months, mean (SD) |             |                                     |                             |        |
| Weight-for-age           | −0.10 (1.24)| −0.16 (1.19)                        | −0.07 (1.27)                | 0.48   |
| Length-for-age           | −1.12 (1.53)| −1.26 (1.41)                        | −1.04 (1.58)                | 0.17   |
| Weight-for-length        | 0.92 (1.44) | 0.94 (1.39)                         | 0.90 (1.48)                 | 0.78   |
| Child feeding practice at 6/10 weeks |         |                                     |                             |        |
| Exclusive breast feeding | 273 (69)    | 97 (70)                             | 176 (68)                    | 0.93   |
| Formula feeding only     | 98 (25)     | 34 (24)                             | 64 (25)                     |        |
| Mixed breastfeeding and other | 24 (6)  | 8 (6)                               | 16 (7)                      |        |
| Child feeding practice at 6 months |         |                                     |                             |        |
| Exclusive breast feeding | 125 (32)    | 42 (30)                             | 83 (32)                     | 0.10   |
| Formula feeding only     | 246 (62)    | 93 (67)                             | 153 (60)                    |        |
| Mixed breastfeeding and other | 24 (6)  | 4 (3)                               | 20 (8)                      |        |

IQR Interquartile range; n number of participants* n for WLHIV = 395

Fig. 2 Growth pattern of infants who are HEU and HU from Cape Town, South Africa and Lusaka, Zambia
We tested for an interaction between infant feeding practice and country comparing infants who were HEU with HU and observed that mean WAZ and WLZ were not altered by different feeding practices in the two countries. While our study, and other studies have reported lower WAZ among infants who were HEU born to women receiving ART in pregnancy compared to infants born to women without HIV [5, 7, 9, 19, 34], the aetiology of differences in growth from birth and timing of catch-up in growth between infants who are HEU compared to those who are HU requires further investigation. While equipoise no longer exists to conduct a randomized trial of timing of fetal ARV exposure, large, well designed studies that equally evaluate biological, social, and structural aetiologies would advance confidence in identifying the safest ARV regimens for use in pregnancy and may identify modifiable risk factors to ensure that birth anthropometrics and growth is comparable between infants who were HEU and those who are HU.

Pooling of data suggested the absence of significant differences in LAZ at 6 to 10 weeks by infant HIV exposure status. Yet poorer linear growth was observed among infants who were HEU compared to those who are HU, despite the absence of significant differences in WAZ and WLZ at this time point between the two groups. Whether this finding reflects foetal programming following exposure to either HIV or ARVs versus more sustained inadequacy of gestational nutritional needs requires further investigation. In a Brazilian birth cohort [17], it is cause of concern that longer follow-up through 24 months of life demonstrated persistently poorer linear growth among children who were HEU compared to those who were HU. We noted that child growth trajectories differed by country, highlighting the importance of studying contextual influences on outcomes of infants who are HEU.

Although we did not find any difference for WAZ, LAZ and WLZ between infants who were exposed to ARVs
from conception compared to those exposed later in gestation, the association between in-utero ARV exposure and adverse growth beyond infancy is not clear [5, 9, 19, 34]. There is still uncertainty as whether an association exists between a specific ARV drug or regimen and poorer growth in infants who are HEU. In our study, the majority of women received an efavirenz (EFV)-containing regimen, precluding robust analysis of differences in infant growth by maternal ARV regimen.

In our cohort, the percentage of infants who were HEU and more likely to be underweight at 6 to 10 weeks of life was higher compared to infants who were HU and this persisted through 6 months of life. However, the proportion of infants who were underweight at 6 months was lower. This may be explained by infant feeding practices, as a higher proportion of infants who were HEU had switched from exclusive breastfeeding to formula feeding by 6 months. It is concerning that breastfeeding durations were short, particularly among infants who were HEU. Our findings are consistent with a study from Botswana [9], Brazil [17] and South Africa [5], where LAZ scores were lower from 6 months of life. This decline in LAZ could be coinciding with early weaning of infants from exclusive breastfeeding because we did not observe the decline when we restricted the analysis to infants who were exclusively breastfeeding by 6 months. This finding of similar growth pattern between infants who were HEU and HU who were exclusively breastfeeding at 6 months is reassuring given the exposure to ARVs in-utero and through the breastfeeding period. However, there is need for further studies to quantify optimal length of breastfeeding for infants who were HEU.

This study had limitations. We could not assess intrauterine growth restriction because of lack of robust measurement for gestational age at birth for both countries. We limited our analysis to mother-infant pairs who had data at all three time points, potentially introducing a survival bias that precluded the detection of growth differences between infants who were HEU and those who were HU. Unmeasured confounding is always a concern with observational research and differences between mothers with and without HIV could not be fully reconciled. However, efforts were made to minimise confounding in our study design and analysis. Additionally, inclusion of a comparator group of women without HIV and their children from the same communities as the WLHIV minimized socio-demographic differences. While we may have had greater

### Table 3: Linear mixed effects models for comparison of WAZ, LAZ and WLZ between infants who were HEU and HU at 6–10 weeks and 6 months

| Anthropometric Measure         | Predictor | N   | Multivariable at 6–10 weeks | Multivariable at 6 months |
|-------------------------------|-----------|-----|----------------------------|--------------------------|
|                               |           |     | β (95% CI)                  | β (95% CI)               |
|                               |           |     | P-value                     | P-value                  |
| *Combined                      |           |     |                             |                          |
| Weight for age z-score        | HU        | 378 | Ref                         |                          |
|                               | HEU       | 395 | −0.29 (−0.46 - 0.12)        | 0.001                    |
|                               |           |     | −0.09 (−0.27 - 0.08)        | 0.31                     |
| Length for age z-score        | HU        | 378 | Ref                         |                          |
|                               | HEU       | 395 | −0.01 (−0.20 - 0.21)        | 0.96                     |
|                               |           |     | −0.28 (−0.50 - 0.06)        | 0.01                     |
| Weight for length z-score     | HU        | 378 | Ref                         |                          |
|                               | HEU       | 395 | −0.42 (−0.68 - 0.16)        | 0.002                    |
|                               |           |     | +0.11 (−0.11 - +0.33)       | 0.32                     |
| South Africa                  |           |     |                             |                          |
| Weight for age z-score        | HU        | 251 | Ref                         |                          |
|                               | HEU       | 246 | −0.23 (−0.47 - 0.01)        | 0.04                     |
|                               |           |     | −0.11 (−0.35 - +0.13)       | 0.36                     |
| Length for age z-score        | HU        | 251 | Ref                         |                          |
|                               | HEU       | 246 | −0.15 (−0.42 - 0.11)        | 0.25                     |
|                               |           |     | −0.30 (−0.59 - 0.01)        | 0.04                     |
| Weight for length z-score     | HU        | 251 | Ref                         |                          |
|                               | HEU       | 246 | −0.15 (−0.47 - +0.16)       | 0.34                     |
|                               |           |     | +0.10 (−0.19 - +0.39)       | 0.51                     |
| Zambia                        |           |     |                             |                          |
| Weight for age z-score        | HU        | 127 | Ref                         |                          |
|                               | HEU       | 149 | −0.31 (−0.59 - 0.04)        | 0.02                     |
|                               |           |     | −0.09 (−0.34 - + 0.16)      | 0.48                     |
| Length for age z-score        | HU        | 127 | Ref                         |                          |
|                               | HEU       | 149 | +0.34 (+0.01 - + 0.68)      | 0.04                     |
|                               |           |     | −0.22 (−0.58 - + 0.14)      | 0.23                     |
| Weight for length z-score     | HU        | 127 | Ref                         |                          |
|                               | HEU       | 149 | −0.92 (−1.39 - -0.44)       | < 0.001                  |
|                               |           |     | +0.08 (−0.26 - + 0.42)      | 0.64                     |

*Combined Weight for age z‑score HU 378 Ref Ref
*Combined Weight for age z‑score HEU 395 Ref Ref
*Combined Length for age z‑score HU 378 Ref Ref
*Combined Length for age z‑score HEU 395 Ref Ref
*Combined Weight for length z‑score HU 378 Ref Ref
*Combined Weight for length z‑score HEU 395 Ref Ref

HEU Infants who are HIV exposed uninfected; HU Infants who are HIV unexposed uninfected; β mean change in z‑score between HEU and HU; CI confidence interval; N number of participants

Adjusted for maternal age, maternal Body Mass Index (BMI), employment, marital status and infant feeding with random intercept for country
Table 4  Liner mixed effect models for comparison of WAZ, LAZ and WLZ at 6–10 weeks and 6 months between infants who were HEU with different timing of fetal ARV exposure

| Anthropometric Measure | Predictor - ARV exposure | N   | Multivariable at 6–10 weeks β (95% CI) | P-value | Multivariable at 6 months β (95% CI) | P-value |
|------------------------|--------------------------|-----|----------------------------------------|---------|--------------------------------------|---------|
| *Combined              | Weight for age z-score   | 139 | +0.02 (−0.21 — +0.26)                  | 0.83    | +0.04 (−0.20 — +0.28)                | 0.73    |
|                        | From conception          | 256 | −0.24 (−0.53 — +0.04)                  | 0.09    | +0.13 (−0.18 — +0.44)                | 0.41    |
| South Africa           | Weight for age z-score   | 74  |                                       |         |                                       |         |
|                        | From conception          | 172 | 0.08 (−0.24 — +0.40)                  | 0.61    | 0.01 (−0.32 — +0.35)                | 0.94    |
| Zambia                 | Weight for age z-score   | 65  |                                       |         |                                       |         |
|                        | From conception          | 84  | −0.11 (−0.48 — +0.27)                  | 0.58    | 0.06 (−0.31 — +0.43)                | 0.74    |
|                        | Length for age z-score   | 65  |                                       |         |                                       |         |
|                        | From conception          | 84  | −0.15 (−0.61 — +0.30)                  | 0.51    | 0.26 (−0.25 — +0.78)                | 0.31    |
|                        | Weight for length z-score| 65  |                                       |         |                                       |         |
|                        | From conception          | 84  | −0.04 (−0.61 — +0.68)                  | 0.90    | −0.09 (−0.71 — +0.39)                | 0.71    |

Adjusted for maternal age, maternal bmi, employment, marital status and infant feeding with random intercept for country.
Model limited to infants who are HIV-exposed uninfected by timing to exposure to ARVs.
β mean change in z-score between infants who are HEU and HU; CI confidence interval; N number of participants.

power to detect true differences in anthropometrics by HIV-exposure groups, contextual differences between the two countries masked significant differences present at a single country. Maternal education and employment status were differently distributed in women living with HIV compared to women without HIV between the two countries. We also noted differences in feeding practices between infants who were HEU compared to HU at 6 months in South Africa, but this was not the same in Zambia. These contrasting circumstances could have influenced growth patterns in opposite direction for infants who were HEU compared to HU between South Africa and Zambia as observed in our study.

Conclusion
In our study, infant growth trajectories differed by country, highlighting the importance of studying contextual influences when conducting outcomes research for the population of infants who are HEU. While pooling of data increases the power to detect small but clinically meaningful differences, studies that rely upon pooling data need to find sound approaches to measurement of contextual heterogeneity between sites for exposures directly associated with the outcome or which mediate the outcome of interest. More data and longer periods of evaluation are needed to ensure that infants who were HEU are achieving comparable growth outcomes to infants born to women without HIV.

Abbreviations
ANC: Antenatal clinic; ARV: Antiretroviral; ART: Antiretroviral therapy; GA: Gestational age; HEU: HIV-exposed uninfected; HU: HIV-unexposed; LAZ: Length-for-age; WLHIV: Women living with HIV; WAZ: Weight-for-age; WLZ: Weight-for-length; SD: Standard deviation.

Supplementary Information
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Additional file 1. Supplementary material
Additional file 2: Table S1. Characteristics of women and infants by HIV status and site at 6/10 weeks and 6 months in Cape Town, South Africa and Lusaka, Zambia.
Additional file 3: Table S2. Linear mixed effects models for comparison of WAZ, LAZ and WLZ at 6–10 weeks and 6 months of life among infants exclusively breastfed for 6 months of life by infant HIV exposure status.

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Authors’ contributions
DCN, EK, MJV and KP collaborated in the writing of the manuscript. DCN, EK, MJV, MMM, MM, CBM, AS, HPM, MD, AB, LM and KP designed and conducted the study and data collection. DCN and KP determined the hypotheses to be tested. DCN performed the statistical analyses. DCN, EK, MJV, MMM, MM, CBM, AS, HPM, MD, AB, LM and KP reviewed the manuscript before submission. The author(s) read and approved the final manuscript.

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Availability of data and materials
The datasets used and analysed during this current study are available from corresponding author on request.

Declarations

Ethics approval and consent to participate
This study was approved by the University of Cape Town’s Faculty of Health Sciences Research Ethics Committee (UCT-HREC) and University of Zambia Biomedical Research Ethics Committee. The respondents participating in the study were adequately informed using participant’s informed written consent statement about the relevant aspects of the study including its aim, interview procedure, anticipated benefits and potential hazards. All women participating in the study provided informed written consent for their own participation and that of their infant’s. All methods in this study were carried out in accordance with relevant guidelines and regulations in the Helsinki Declaration as revised in 1983.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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