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# Higher prevalence of stunting and poor growth outcomes in HIV-exposed uninfected than HIV-unexposed infants in Kenya

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## Abstract

**Background:** With the growing population of HIV-exposed uninfected (HEU) children globally, it is important to determine population-level growth differences between HEU and HIV-unexposed uninfected (HUU) children.

**Methods:** We analyzed data from a population-level survey enrolling mother-infant pairs attending 6-week and 9-month immunizations in 140 clinics across Kenya. Weight-for-age (WAZ), length-for-age (LAZ), head circumference-for-age (HCAZ) z-scores and underweight (WAZ<−2), stunting (LAZ<−2), and microcephaly (HCAZ<−2), were compared between HEU and HUU. Correlates of growth faltering and poor growth were assessed using generalized Poisson and linear regression models.

**Results:** Among 2,457 infants, 456 (19%) were HEU. Among mothers living with HIV, 64% received antiretroviral therapy and 22% were on antiretroviral prophylaxis during pregnancy. At 9-months, 72% of HEU and 98% of HUU were breastfeeding. At 6-weeks, HEU had lower mean WAZ (−0.41 vs. −0.09; p<0.001) and LAZ (−0.99 vs. −0.31; p=0.001) than HUU. Stunting was higher in HEU than HUU at 6-weeks (34% vs 18%, p<0.001) and 9-months (20% vs 10%, p<0.001). In multivariable analyses, HEU had lower mean LAZ at 6-weeks (−0.67, 95%CI: −1.07, −0.26) and 9-months (−0.57, 95%CI: −0.92, −0.21) and HEU had higher stunting prevalence (week-6 adjusted prevalence ratio [aPR]: 1.88, 95%CI: 1.35, 2.63; month-9 aPR: 2.10, 95%CI:

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1.41, 3.13). HEU had lower mean head circumference (−0.49, 95%CI: −0.91, −0.07) and higher prevalence of microcephaly (aPR: 2.21, 95%CI: 1.11, 4.41) at 9-months.

**Conclusion:** Despite high maternal ART coverage, HEU had poorer growth than HUU in this large population-level comparison. Optimizing breastfeeding practices in HEU may be useful to improve growth.

### Keywords

HIV; growth; stunting; HIV-exposed uninfected children

## INTRODUCTION

High coverage of combination antiretroviral therapy (cART) among pregnant and breastfeeding women with HIV (WHIV) has resulted in an expanding population of HIV-exposed uninfected (HEU) children globally.[1] HEU have been shown to have poorer growth and health outcomes than HIV unexposed uninfected children (HUU).[2–6] Limited evidence also suggests that HEU may be at increased risk of microcephaly,[7,8] which may have long-term consequences on neurocognitive development. Underlying mechanisms for these differences remain unclear. Studies evaluating in-utero ART exposure and child growth have mixed results and vary by age.[9–11] HIV exposure has been associated with immunological vulnerabilities and lower birthweight, both of which adversely affect growth. Household and socioeconomic differences adversely affect child growth, and these inequalities may play a larger role in children born to WHIV, particularly in low and middle-income countries.[12] Population-level data on child head circumference, length, and weight in high HIV burden settings is warranted.

## METHODS

### Study design and population

We used data from two facility-based cross-sectional surveys evaluating prevention of mother-to-child transmission (PMTCT) programs at 140 clinics in Kenya from July-December 2013. The primary survey used probability-proportional-to-size sampling to select 120 clinics. A second survey oversampled WHIV at 30 randomly selected clinics in Nyanza province. Mother-infant pairs attending 6-week and 9-month immunizations were eligible, as previously described.[13]

### Data collection

Staff administered a standardized questionnaire including sociodemographic characteristics, maternal ART or antiretroviral prophylaxis (ARVs), birth outcomes, breastfeeding, and infant ARVs and HIV testing. Staff measured weight, length/height, head circumference, and mid-upper arm circumference of mothers and infants. Mothers self-reporting HIV-positive status had their results confirmed with the Maternal and Child Health booklet. Dried blood spot samples were collected from HIV-exposed infants for HIV DNA PCR testing and results returned to the facility.

### Ethical Considerations

This study was approved by ethical review boards at the Kenya Medical Research Institute and University of Washington and reviewed in accordance with the U.S. Centers for Disease Control and Prevention human research protection procedures. Informed written consent was collected from all participants prior to study procedures.

### Growth outcomes

The World Health Organization's Anthro software was used to calculate weight-for-age (WAZ), length-for-age (LAZ), and head circumference-for-age (HCAZ) z-scores.[14] Implausible measures were excluded if: WAZ <−6 or >5, LAZ <−6 or >6, or HCAZ <−5 or >5. Primary outcomes included continuous growth (WAZ, LAZ, HCAZ) and growth faltering defined as z-score <−2 [underweight (WAZ<−2), stunting (LAZ<−2), microcephaly (HCAZ<−2)].

### Statistical analysis

All infants with growth data at week-6 or month-9 immunizations were included in the analysis. Women and infants newly diagnosed with HIV at the study visit were excluded, as timing of infant HIV exposure could not be accurately determined. Rao-Scott chi-square tests were used to compare associations and Student's t-tests were used to compare means. Generalized linear models with a Gaussian distribution were used to examine independent correlates of continuous growth outcomes. Poisson regression was used to determine prevalence ratios (PR) and 95% confidence intervals (95%CI). Covariates associated with poor growth at $p<0.05$ in univariate analysis were included in multivariate models. Low birthweight was not included in multivariate models because it lies in the causal pathway; however, sensitivity analyses including low birthweight in multivariate models yielded similar results (Supplementary Table 3). Analyses accounted for clinic-level clustering and were conducted using STATA 14 (STATA Corporations, College Station, Texas).

## RESULTS

Of 2,457 infants surveyed, 456 (18.6%) were HEU, of whom 50.7% attended clinic for 6-week and 49.3% for 9-month immunizations. HEU at 6-weeks had lower mean birthweight and fewer were currently breastfeeding at 6-weeks and 9-months compared to HUU. WHIV were older and had completed less education than mothers without HIV at both timepoints (Table 1).

Forty-three percent of WHIV were on cART prior to the pregnancy. Sixty-four percent received cART and 22.4% received ARVs during pregnancy. Overall, 13.2% of WHIV did not receive ART or ARVs during pregnancy. Most women on ART were on non-nucleoside reverse transcriptase inhibitors-based (NNRTI) regimens. Most (97.8%) HEU received nevirapine for PMTCT and 96.9% of HEU attending 9-month immunizations had received cotrimoxazole prophylaxis.

### Weight-for-age z-scores and underweight

HEU had a significantly lower mean WAZ than HUU at 6-weeks (−0.41, 95%CI: −0.58, −0.24 vs. −0.09, 95%CI: −0.19, 0.01; p<0.001), but WAZ was not significantly different between HEU and HUU at 9-months (−0.38 95%CI: −0.55, −0.21 vs. −0.21 95%CI: −0.33, −0.10; p=0.10). At 6-weeks, HEU had significantly lower mean WAZ than HUU, after adjusting for hospitalization and maternal BMI (Table 2). HIV exposure was not associated with mean WAZ at 9-months or underweight at 6-weeks or 9-months. Similar proportions of HEU and HUU were underweight at 6-weeks (7% vs. 5%, p=0.36) and 9-months (12% vs. 8%; p=0.07).

### Length for age z-score and stunting

Mean LAZ was significantly lower in HEU than HUU at 6-weeks (−0.99, 95%CI: −1.39, −0.58 vs. −0.31 95%CI: −0.55, −0.07; p=0.001) and 9-months (−0.60 95%CI: −0.94, −0.26 vs. −0.07 95%CI: −0.25, 0.12; p=0.005). In multivariate analyses, HIV exposure was associated with lower mean LAZ at 6-weeks and 9-months (Table 2). One-third (34%) of HEU were stunted at 6-weeks compared to 18% of HUU (p<0.001). At 9-months, 20% of HEU were stunted compared to 10% of HUU (p<0.001). HIV exposure was significantly associated with higher stunting prevalence at 6-weeks and 9-months in adjusted analyses (Table 2).

### Head circumference-for-age z-scores and microcephaly

Mean HCAZ (0.56, 95%CI: 0.30, 0.81 vs. 0.77, 95%CI: 0.63, 0.92; p=0.11) was similar between HEU and HUU at 6-weeks, but HEU had lower mean HCAZ (−0.10, 95%CI: −0.52, 0.31 vs. 0.41 95%CI: 0.26, 0.56; p=0.018) at 9-months. At 6-weeks, microcephaly prevalence was similar among HEU and HUU (2% vs. 3%; p=0.68). At 9-months, 14% of HEU had microcephaly versus 7% of HUU (p=0.025). HIV exposure was associated with lower mean HCAZ and microcephaly in univariate and multivariate analyses at 9-months (Table 2).

### Maternal ART

In a sensitivity analysis comparing only HEU mothers on cART during pregnancy to HUU, primary results remained largely unchanged (Supplementary Table 4).

Among HEU, maternal cART before pregnancy and maternal cART or ARVs during pregnancy were not associated with growth at week 6. At month-9, maternal cART before pregnancy was univariately associated with lower mean WAZ and underweight in HEU. Among HEU at 9-months, maternal cART before pregnancy was univariately associated with lower mean LAZ and stunting compared to no maternal ART. Maternal ART or ARVs during pregnancy was not associated with growth at 9-months (Supplementary Table 1 and Figure 1).

## DISCUSSION

In this population-level analysis, HEU had poor weight and length growth compared to HUU, and stunting was twice as prevalent in HEU at 6-weeks and 9-months. At 9-months,

HEU had higher prevalence of microcephaly and lower mean head circumference than their HUU peers.

These findings are consistent with other studies in sub-Saharan Africa reporting poor early growth in HEU compared to HUU.[2,4,5,15–17] Independent of HIV status, breastfeeding was associated with 72% lower prevalence of underweight at 6-weeks and prior hospitalization was associated with underweight at 6-weeks and 9-months. HEU have greater risk of low birthweight[2,15,18–20] and diarrhea, pneumonia, and hospitalization in early infancy than HUU,[21] which impacts WAZ and LAZ. Our data are consistent with longitudinal studies showing greater variability in weight velocity during infancy and suggest other factors may play a more pivotal role in weight growth. Child stunting has been associated with socioeconomic, dietary, health, and environmental factors[22] and increased morbidity and mortality.[23] While large-scale interventions to strengthen infant and young child feeding practices have led to reductions in early stunting,[24,25] nutritional interventions alone may not be able to prevent or reverse stunting.[16] Understanding relevant socioeconomic and biological mechanisms for early length growth are important to refine interventions to reduce stunting in HEU.

Among children screened at 9-months, HEU had lower mean head circumference and microcephaly prevalence was twice as common. While the limited discussion on microcephaly in HEU has focused on maternal cART, we found that shorter maternal height and lower education were independently associated with microcephaly irrespective of HIV exposure. Both a pre-ART study in Zimbabwe and a study of HEU born to mothers on cART in Nigeria reported higher prevalence of microcephaly among HEU than HUU.[4,8] Recently, the U.S.-based SMARTT study reported lower neurodevelopmental scores in HEU with microcephaly.[7] Our results showed no association between cART prior to or during pregnancy and poor head growth. Further studies are needed to better understand the population prevalence and drivers of microcephaly in early childhood.

Maternal characteristics, including lower height, BMI, and education have been associated with poor growth,[26,27] which is consistent with our findings. Strategies to reduce poverty and promote maternal health and education are needed to improve child growth. Strengthening relationships between health facilities and community programs could help to address some of the socioeconomic and psychosocial challenges faced by families of HEU.

HEU may be at higher risk of growth faltering due to immune activation,[28] alterations in the gut microbiome, and systemic inflammation due to in-utero or postnatal exposure to HIV and prolonged exposure to ART despite their HIV negative status.[9–11,29] We found that pre-pregnancy maternal ART was associated with lower length, lower weight, underweight, and stunting at 9 months, suggesting that peri-conception ART may have long-term impact on growth in HEU. It is likely this may differ by regimen; further studies evaluating the role of pre-conception ART on long-term growth are warranted.

This evaluation enrolled mother-infant pairs in 140 facilities across Kenya, allowing for a better understanding of growth among children in urban and rural settings. A sensitivity analysis including data from only the primary survey had similar findings

(Supplementary Table 2). While mother-infant pairs not presenting to clinic were not captured, UNICEF estimated that 95% of living children received their first dose of Diphtheria-Tetanus-Pertussis vaccine immunization (6-week) and 94% of living children receive their first dose of measles vaccine (9-month) in 2013.[30] This study was conducted at facilities, and HIV-affected families could have higher engagement in care, resulting in a potential underestimation of differences between HEU and HUU children. In this study, mothers were on NNRTI regimens – further investigation on the impact of integrase inhibitor-based regimens, including dolutegravir, on growth among HEU is warranted, as dolutegravir has been associated with increased BMI[31–34] and higher pregnancy BMI has been associated with adverse infant outcomes.[35] While this study was conducted prior to WHO recommendations for universal ART, the majority of mothers received cART and recent studies continue to show poor growth in HEU.[2–5] In a sensitivity analysis restricted to only HEU with mothers on cART, we showed similar growth deficits in HEU.

Findings from this population-level comparison of HEU and HUU support existing evidence that HEU have poor length and weight growth in early childhood and add to the limited data on poor head growth in these children. Strategies to optimize breastfeeding and improve nutritional practices in HEU may improve long-term growth outcomes in this growing and vulnerable population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1.**

Characteristics of HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) infants and their mothers at week 6 and month 9 immunization visits at randomly selected clinics in Kenya

| | % (95% CI) or Mean (95% CI) | | | | | |
|---|---|---|---|---|---|---|
| | 6-week immunization visit | | | 9-month immunization visit | | |
| | HEU (n=231) | HUU (n=1,178) | P-value | HEU (n=225) | HUU (n=823) | P-value |
| ***Infant Characteristics:*** | | | | | | |
| Age (weeks) | 5.6 (5.6, 5.7) | 5.8 (5.7, 6.0) | 0.04 | 36.6 (36.0, 37.1) | 36.3 (35.9, 36.7) | 0.42 |
| Male | 51.5 (46.9, 56.2) | 50.3 (47.4, 53.1) | 0.66 | 47.6 (42.7, 52.4) | 51.6 (48.3, 55.0) | 0.19 |
| Birth weight (kg) | 3.11 (3.03, 3.19) | 3.23 (3.19, 3.27) | 0.009 | 3.24 (3.14, 3.34) | 3.25 (3.21, 3.29) | 0.81 |
| MUAC | - | - | - | 14.2 (13.9, 14.5) | 14.2 (13.9, 14.5) | 0.79 |
| Currently breastfeeding | 96.1 (92.1, 98.1) | 99.9 (99.4, 100.0) | <0.001 | 72.4 (62.6, 80.5) | 98.2 (97.0, 98.9) | <0.001 |
| Prior hospitalization | 2.6 (0.9, 7.3) | 4.5 (3.3, 6.2) | 0.28 | 11.6 (6.8, 18.9) | 12.2 (9.3, 15.7) | 0.86 |
| Cotrimoxazole * | - | - | - | 96.9 (91.6, 98.9) | - | - |
| Nevirapine for PMTCT | 97.4 (94.4, 98.8) | - | - | 98.2 (95.3, 99.3) | - | - |
| ***Maternal Characteristics:*** | | | | | | |
| Age (years) | 28.0 (27.3, 28.7) | 25.3 (25.0, 25.7) | <0.001 | 28.8 (28.1, 29.4) | 25.8 (25.4, 26.3) | <0.001 |
| Primary education and below (ref: above primary) | 67.1 (59.6, 73.8) | 51.5 (47.5, 55.6) | <0.001 | 62.2 (55.6, 68.5) | 52.3 (47.0, 57.5) | 0.02 |
| Number of children | 3.0 (2.8, 3.2) | 2.9 (2.8, 3.1) | 0.69 | 3.2 (3.0, 3.4) | 2.9 (2.7, 3.1) | 0.06 |
| Married/cohabiting | 84.4 (78.3, 89.1) | 86.5 (84.1, 88.6) | 0.47 | 81.3 (76.4, 85.4) | 87.6 (84.8, 90.0) | 0.01 |
| Body mass index (kg/m$^2$) | 23.2 (22.6, 23.8) | 23.7 (23.3, 24.1) | 0.08 | 23.5 (23.0, 24.0) | 23.7 (23.3, 24.1) | 0.57 |
| Height (cm) | 160.3 (159.0, 161.6) | 160.4 (159.5, 161.3) | 0.85 | 161.3 (159.9, 162.7) | 160.5 (159.6, 161.3) | 0.30 |
| Crowding (≥3 per room) | 42.4 (35.0, 50.3) | 41.0 (35.7, 46.5) | 0.74 | 47.6 (40.4, 54.8) | 42.4 (37.7, 47.3) | 0.22 |
| cART before pregnancy | 45.5 (38.3, 52.8) | - | - | 40.4 (34.5, 46.7) | - | - |
| ARVs during pregnancy | | | | | | |
| Combination ART | 68.0 (60.1, 75.0) | - | - | 60.9 (52.6, 68.6) | - | - |
| Monotherapy (AZT) | 17.8 (12.4, 24.7) | - | - | 27.1 (19.4, 36.5) | - | - |
| No ART or ARVs | 14.3 (9.2, 21.5) | - | - | 12.0 (7.7, 18.2) | - | - |

* Cotrimoxazole initiated at 6-week immunization visit

Abbreviations: ART, antiretroviral therapy; ARVs, antiretroviral drugs; AZT, zidovudine; MUAC, mid upper arm circumference

**Table 2.**

Multivariable analysis of association between growth among infants at week 6 and month 9 immunizations at randomly selected clinics in Kenya

| | Underweight | | | Stunting | | | Low head circumference | | |
|---|---|---|---|---|---|---|---|---|---|
| | **aPR** | **(95% CI)** | ***P*** | **aPR** | **(95% CI)** | ***P*** | **aPR** | **(95% CI)** | ***P*** |
| **Week 6 Immunization Visit** | | | | | | | | | |
| HEU infant (ref: HUU) | 1.22 | (0.71, 2.10) | 0.471 | 1.88 | (1.35, 2.63) | <0.001 | 0.86 | (0.32, 2.28) | 0.762 |
| Prior hospitalization infant (ref: no) | 3.32 | (1.67, 6.59) | 0.001 | - | - | - | 5.24 | (2.25, 12.24) | <0.001 |
| Currently breastfeeding (ref: no) | 0.27 | (0.09, 0.83) | 0.023 | - | - | - | - | - | - |
| Crowding (ref: <3 per room) | 1.79 | (1.15, 2.77) | 0.010 | - | - | - | 1.94 | (0.98, 3.84) | 0.057 |
| **Month 9 Immunization Visit** | | | | | | | | | |
| HEU infant (ref: HUU) | 1.26 | (0.85, 1.87) | 0.257 | 2.10 | (1.41, 3.13) | <0.001 | 2.21 | (1.11, 4.41) | 0.024 |
| Male infant (ref: female) | 1.76 | (1.11, 2.79) | 0.016 | - | - | - | - | - | - |
| Prior hospitalization infant (ref: no) | 1.63 | (1.01, 2.64) | 0.045 | - | - | - | - | - | - |
| Currently breastfeeding (ref: no) | 0.65 | (0.38, 1.13) | 0.126 | - | - | - | - | - | - |
| Maternal height (cm) | - | - | - | 0.97 | (0.95, 0.99) | 0.016 | - | - | - |
| | **WAZ** | | | **LAZ** | | | **HCAZ** | | |
| | **aCoeff** | **(95% CI)** | ***P*** | **aCoeff** | **(95% CI)** | ***P*** | **aCoeff** | **(95% CI)** | ***P*** |
| **Week 6 Immunization Visit** | | | | | | | | | |
| HEU infant (ref: HUU) | −0.31 | (−0.50, −0.12) | 0.001 | −0.67 | (−1.07, −0.26) | 0.002 | −0.23 | (−0.50, 0.04) | 0.098 |
| Prior hospitalization infant (ref: no) | −0.61 | (−1.06, −0.16) | 0.008 | - | - | - | −0.58 | (−1.12, −0.04) | 0.036 |
| Maternal height (cm) | - | - | - | 0.03 | (0.01, 0.05) | 0.009 | 0.02 | (0.00, 0.03) | 0.019 |
| Maternal BMI | 0.04 | (0.02, 0.06) | <0.001 | - | - | - | - | - | - |
| **Month 9 Immunization Visit** | | | | | | | | | |
| HEU infant (ref: HUU) | −0.15 | (−0.35, 0.05) | 0.131 | −0.57 | (−0.92, −0.21) | 0.002 | −0.49 | (−0.91, −0.07) | 0.022 |
| Male infant (ref: female) | −0.22 | (−0.41, −0.03) | 0.021 | −0.45 | (−0.68, −0.21) | <0.001 | −0.23 | (−0.46, −0.01) | 0.044 |
| Prior hospitalization infant (ref: no) | −0.27 | (−0.53, 0.003) | 0.053 | - | - | - | - | - | - |
| Maternal height (cm) * | - | - | - | 0.02 | (0.01, 0.04) | 0.005 | - | - | - |
| Maternal BMI | 0.03 | (0.01, 0.05) | 0.003 | - | - | - | 0.04 | (0.02, 0.06) | 0.001 |
| Maternal primary education and below (ref: above primary) | -0.10 | (−0.26, 0.07) | 0.241 | - | - | - | -0.24 | (−0.45, −0.04) | 0.021 |

| | Underweight | | | Stunting | | | Low head circumference | | |
|---|---|---|---|---|---|---|---|---|---|
| | **aPR** | **(95% CI)** | ***P*** | **aPR** | **(95% CI)** | ***P*** | **aPR** | **(95% CI)** | ***P*** |
| Crowding (ref: <3 per room) | -0.26 | (−0.43, −0.10) | 0.002 | - | - | - | - | - | - |

*Maternal BMI and height were not included in the same multivariate model – only BMI was included for WAZ and HCAZ and only maternal height was included for LAZ;

Abbreviations: BMI: body mass index, HEU: HIV-exposed uninfected, HUU: HIV-unexposed uninfected