A 12-month Prospective Study of HIV-infected and HIV-uninfected Women and Their Infants in Malawi: Comparative Analysis of Clinical Events and Infant Growth

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Abstract. Few studies have compared clinical outcomes in HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) infants in the current scenario of universal and lifelong maternal antiretroviral therapy (ART). HIV-uninfected and HIV-infected Malawian women receiving ART and their breastfed infants were followed for 12 months postpartum, analyzing the rates of infectious and noninfectious events and assessing infant growth at 6 weeks, 6 months, and 12 months. The cohorts included 227 mothers (70 HIV-negative, 157 HIV-positive) and 235 infants (72 HUU, 163 HEU). No maternal or infant deaths occurred during follow-up. HIV-negative women were less likely to complete follow-up (48.6% versus 91.1%). Mothers with and without HIV had similar rates of both infectious and noninfectious events per person-month. Infants who were HEU, compared with HUU, had higher rates of events of any type, lower respiratory tract infections (LRTI), and noninfectious events. HEU had lower body mass index (BMI) at 6 weeks but did not differ from HUU in all anthropometric measures at 6 and 12 months; in growth between 6 weeks and 12 months; and in occurrence of stunting, underweight, and wasting at 6 weeks, 6 months, and 12 months. During the first year of life, infants who were HEU, compared with HUU, showed a transiently lower BMI and an increased risk of LRTI.

INTRODUCTION

The worldwide expansion of lifelong antiretroviral treatment (ART) in all HIV-infected individuals, including initiation or continuation of ART in pregnant women, has produced, together with a dramatic decline in HIV vertical transmission, a concomitant large increase in the number of HIV-exposed uninfected (HEU) infants.[1] Defining the health status of this population, which includes no fewer than 15 million children worldwide,[2] is therefore an important research priority.

Some studies have reported that HEU infants may experience worse clinical outcomes, compared with HIV-unexposed uninfected (HUU) children. The issue is much debated, however, because not all published studies are consistent.[2–7] Most of the additional morbidity described in HEU is represented by infections, such as lower respiratory tract infections (LRTI), pneumonia, tuberculosis, diarrhea, sepsis, and fungal infections, that can be favored not only by biological factors but also by environmental and socioeconomic conditions.[2,4,8,9] Similar considerations are also possible for the impaired postnatal growth that has been commonly reported in HEU, with variable consistency of findings.[4,10–17] Comparative studies in the era of universal and lifelong maternal ART therapy, when mortality is expected to be low,[9] are limited. To contribute to this issue, we designed a longitudinal cohort study of mother–infant pairs with different maternal HIV status, followed for 1 year postnatally in three health facilities in Malawi.

METHODS

Study population. In this prospective cohort study, we followed HIV-uninfected and HIV-infected Malawian pregnant women receiving ART and their breastfed children from late pregnancy until approximately 12 months postpartum.

Maternal inclusion criteria were age $\geq$ 18, documented HIV test results, gestational age (as reported by the women) between 32 and 36 weeks, willingness to attend monthly visits with the child, and ability to provide informed consent.

Eligible infants were defined as HEU, if they were born to HIV-infected mothers but were HIV-uninfected, and as HUU if they were born to HIV-uninfected mothers (HIV-1 antibody seronegative at delivery).

Study procedures. The study was conducted within the structures of the DREAM (Disease Relief through Excellent and Advanced Means) Program of the Community of S. Egidio, an Italian faith-based non-governmental organization offering health services for HIV, tuberculosis (TB) and noncommunicable diseases in several countries.[18–20]

Women and infants were followed at an urban center in Blantyre and at two periurban sites in the surrounding area (Chileka and Machinjiri). Participation was proposed to all eligible women attending the sites during the study period. Women were enrolled at approximately 36 weeks of gestation and then visited postdelivery with their children, with a first postpartum visit within 2 weeks and subsequent visits at 6 weeks, 10 weeks, and then monthly from month 3 to month 12. Infant body weight and length were measured by trained local staff at the sites. Infant vaccinations followed Malawi National Guidelines.[21] All HIV-infected mothers received antiretroviral therapy according to Malawi's national guidelines.[22,23] All HIV-exposed infants received postexposure prophylaxis with nevirapine for 6 weeks and were prescribed cotrimoxazole from 6 weeks of age.[22] A polymerase chain reaction was performed in infants for HIV-DNA detection at 6 and 48 weeks. In the presence of more than two missed visits and no answer to telephone calls, a trained counselor performed a home visit to trace the woman.

Definitions. Planned postdelivery follow-up time was 12 months. Follow-up time for study analyses was calculated from date of delivery and censored at date of last visit, date of death or at 400 days if its length at last visit exceeded this threshold.

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Feeding was categorized as exclusive breastfeeding (infants who only received breast milk); mixed breastfeeding (infants who received breast milk supplemented with other foods or liquids, including traditional medicines and water), and formula feeding (infants who exclusively received replacement feeds and no breast milk). Mothers were encouraged to breastfeed exclusively during the first 6 months.[24]

Length-for-age, weight-for-age, weight-for-length, and body mass index (BMI) z-scores (LAZ, WAZ, WLZ, and BMIZ, respectively) were calculated using the WHO Anthro Survey Analyzer, excluding values less than –6 and > 6 as implausible.[25] We defined underweight as WAZ less than –2, severe underweight as WAZ less than –3, stunting as LAZ less than –2, severe stunting as LAZ less than –3, wasting as WLZ less than –2, and severe wasting as LAZ less than –3.[4,12]

We considered as infectious events upper respiratory tract infections (URTI) and LRTI, pulmonary and extrapulmonary TB, gastroenteritis, candidiasis, and sepsis. All diagnoses were clinical. For LRTI, patients were evaluated for presence of fever, malaise, cough, pleuritic chest pain, dyspnea. or tachypnoea and by the auscultation of chest, according to existing guidelines.[26]

Sample size determination. For the primary outcome of morbidity (any event) in infants, a sample size of 150 per group was estimated to have 80% power to detect as significant at a $P < 0.05$ level a 12% difference in morbidity between the two groups of infants (20% in HEU compared with 8% in HUU).

Statistical analysis. We compared the clinical and demographic characteristics of women with and without HIV and the clinical characteristics of their infants (HEU and HUU, respectively). For both mothers and infants, we compared the rates of infectious and noninfectious events per month of follow-up. Analysis was restricted to singleton or first-born twins.

Body weight and length, BMI, LAZ, WAZ, WLZ, BMIZ, undernutrition, severe undernutrition, wasting, severe wasting, stunting, and severe stunting were compared in the two groups at 6 weeks, 6 months, and 12 months. Data were summarized as proportions, means with standard deviations (SD), or medians with interquartile ranges (IQR; percentiles 25–75) and compared by the chi-square or the Fisher tests (when expected cell frequencies were < 5) for categorical variables, and by the t-test or the Mann-Whitney U test for quantitative variables. Unadjusted odds ratios (with 95% confidence intervals) for stunting, underweight and wasting were calculated in contingency tables, using the chi-square test for comparisons between groups. Stunting was also analyzed in a multivariable logistic regression model that used as dependent variable its occurrence at any time during follow-up (6 weeks, 6 months, or 12 months) and as independent variables HEU/HUU infant status (included a priori) and other sociodemographic and clinical variables associated to stunting with a P level ≤ 0.15 in univariate analyses previously conducted. In all analyses, P values < 0.05 were considered significant. All analyses were performed using the SPSS software, version 27 (IBM Corp., 2017, Armonk, NY).

RESULTS

Population. Study enrollment started in January 2019 and ended in March 2020. Follow-up ended in June 2021. The initial sample included 233 women with live born infants

(73 HIV negative, 160 HIV positive). Six mother–infant pairs were excluded for the following reasons: lost soon after delivery (three in the HIV-negative group, one in the HIV-positive group), HIV transmission to infant (one in the HIV-positive group), neonatal death before HIV testing (one in the HIV-positive group). The final sample included 227 mothers (70 HIV negative, 157 HIV positive) and 235 infants (53.9% females, 46.1% males, 72 HUU, 163 HEU with negative HIV tests, including two sets of twins from HIV-negative mothers and six sets of twins from HIV-positive mothers). The site in Blantyre enrolled only HIV-positive pregnant women ($n = 61$), whereas the other two sites enrolled both HIV positive (Chileka $n = 35$, Machinjiri $n = 61$) and HIV-negative women (Chileka $n = 39$, Machinjiri $n = 31$). The general characteristics of the two final cohorts of mothers are reported in Table 1. Women with HIV infection were older and more commonly resident in urban areas, but no differences were observed for all the remaining demographic and clinical characteristics.

The majority of the women with HIV ($n = 86$, 54.8%) were already on antiretroviral treatment at conception, 13 (8.3%) started during the first trimester, 53 (33.8%) started during the second trimester, and five (3.2%) during the third trimester. At the end of pregnancy, most of HIV-positive women (120/157, 76.4%) were on tenofovir, lamivudine, and efavirenz (TDF/3TC/EFV), 12 (7.6%) were on tenofovir, lamivudine, and dolutegravir (TDF/3TC/DTG), and 25 (15.9%) were on other regimens.

Postdelivery follow-up of mothers and infants. Overall, 107 mothers (84 HIV positive, 53.5%; 23 HIV negative, 42.9%) brought their infants to visit soon after delivery. The infant postdelivery visit was performed at a median age of 11 days in HEU (IQR: 8–13) and at 10 days in HUU (IQR: 7–14) ($P = 0.464$). At this age median infant weight was 3.6 kg (IQR: 3.2–4.0) in HEU and 3.7 kg (IQR: 3.2–4.1) in HUU ($P = 0.558$), and median infant length was 50 cm (IQR: 48–51.75) in HEU and 48.5 cm (IQR: 48–52) in HUU ($P = 0.790$).

Vaccination status was known for 206 infants (91.2%), and all of them were regularly vaccinated. For the remaining 21 infants, vaccination status was not recorded because of missed follow-up visit attendance. All infants were breastfed, and mixed feeding was introduced at a median age of 6 months (IQR: 6–7) in both HEU and HUU infants ($P = 0.714$).

Follow-up status, follow-up time, rate of events in mothers and infants, and hemoglobin levels are reported in Table 2.

No deaths were observed in the two cohorts of women. Loss to follow-up was significantly higher among HIV-negative women and their HUU infants: mother–infant pairs in this group were significantly less likely to complete the study (48.6% versus 91.1%), had a lower number of postpartum visits attended (5.2 versus 8.5), and showed a significantly shorter follow-up time (8.4 versus 11.6 months) (all P values < 0.001).

In mothers, a total of 354 events were observed during the entire study, of whom 120 were infectious (one malaria, 26 URTI, 57 LRTI, 23 gastroenteritis, two candidiasis, 11 sepsis) and 234 noninfectious, mostly represented by headache ($n = 45$), skin rash ($n = 34$), and musculoskeletal body pains ($n = 27$). No cases of preeclampsia, maternal cholestasis, or gestational diabetes were reported.

Compared with HIV-negative women, a higher proportion of HIV-positive women experienced during the study events

TABLE 1
Population (mothers)

	All women				HIV-positive women				HIV-negative women				P
	n/N	%	Median (IQR)	Mean (SD)	n/N	%	Median (IQR)	Mean (SD)	n/N	%	Median (IQR)	Mean (SD)	
Clinical center													
Blantyre	61/227	26.9	–	–	61/157	38.9	–	–	0/70	0	–	–	< 0.001
Chileka	74/227	32.6	–	–	35/157	22.3	–	–	39/70	55.7	–	–	
Machinjiri	92/227	40.5	–	–	61/157	38.9	–	–	31/70	44.3	–	–	
Residence													
Urban	58/227	25.6	–	–	51/157	32.5	–	–	7/70	10.0	–	–	0.001
Periurban	127/227	55.9	–	–	83/157	52.9	–	–	44/70	62.9	–	–	
Rural	42/227	18.5	–	–	23/157	14.6	–	–	19/70	27.1	–	–	
Electricity in household	108/227	47.6	–	–	79/157	50.3	–	–	29/70	41.4	–	–	0.216
Water in household	139/227	61.2	–	–	91/157	58.0	–	–	48/70	68.6	–	–	0.130
Travel duration to site > 1 hour	63/227	27.8	–	–	48/157	30.6	–	–	15/70	21.4	–	–	0.155
Marital status													
Single/divorced/separated	17/227	7.5	–	–	10/157	6.4	–	–	7/70	10.0	–	–	0.337
Married/cohabiting	210/227	92.5	–	–	147/157	93.6	–	–	63/70	90.0	–	–	
Working status													
Housewife/none	153/227	67.4	–	–	104/157	66.2	–	–	49/70	70.0	–	–	0.821
Trader	23/227	10.1	–	–	17/157	10.8	–	–	6/70	8.6	–	–	
Other job	51/227	22.5	–	–	36/157	22.9	–	–	15/70	21.4	–	–	
Education level													
None	9/227	4.0	–	–	6/157	3.8	–	–	3/70	4.3	–	–	0.718
Primary	86/227	37.9	–	–	56/157	35.7	–	–	30/70	42.9	–	–	
Secondary	120/227	52.9	–	–	87/157	55.4	–	–	33/70	47.1	–	–	
Above secondary	12/227	5.3	–	–	8/157	5.1	–	–	4/70	5.7	–	–	
Place of delivery													
Home	2/224	0.9	–	–	1/157	0.6	–	–	1/67	1.5	–	–	0.173
Hospital	80/224	35.7	–	–	62/157	39.5	–	–	18/67	26.9	–	–	
Health center	142/224	63.4	–	–	94/157	59.9	–	–	48/67	71.6	–	–	
Mode of delivery													
Caesarean	27/224	12.1	–	–	20/157	12.7	–	–	7/67	10.4	–	–	0.630
Vaginal	197/224	87.9	–	–	137/157	87.3	–	–	60/67	89.6	–	–	
Age (years) (n = 227)	–	–	29 (24–33)	28.8 (6.1)	–	–	30 (25–34)	29.7 (5.8)	–	–	25 (20.7–32.0)	26.4 (6.3)	< 0.001
No. of children in household (n = 227)	–	–	2 (1–3)	2.1 (1.4)	–	–	2 (1–3)	2.0 (1.4)	–	–	2 (1–3)	2.2 (1.5)	0.422
Hb (g/dL) (n = 120)	–	–	11.0 (9.9–11.9)	10.9 (1.3)	–	–	10.9 (9.9–11.9)	10.8 (1.3)	–	–	11.9 (10.2–12.6)	11.4 (1.4)	0.140
BMI (kg/m²) (n = 198)*	–	–	23.3 (21.2–25.8)	23.8 (3.9)	–	–	23.1 (21.3–25.9)	23.8 (3.8)	–	–	24.8 (20.9–25.5)	24.1 (4.1)	0.640

BMI = body mass index; Hb = hemoglobin; IQR = interquartile range (between 25 and 75 percentile).
* Measured at 1 month postpartum.

TABLE 2
Follow-up and clinical events for mothers and infants

	All women/infants			HIV-positive women/HEU infants			HIV-negative women/HUU infants			
	n/N	%	Mean (SD)	n/N	%	Mean (SD)	n/N	%	Mean (SD)	P
Follow-up (mother and infants)										
Study completed*	177/227	78.0	–	143/157	91.1	–	34/70	48.6	–	< 0.001
No. of visits attended	–	–	7.5 (3.1)	–	–	8.5 (2.5)	–	–	5.2 (3.1)	< 0.001
Months of follow-up	–	–	10.6 (3.5)	–	–	11.6 (2.4)	–	–	8.4 (4.5)	< 0.001
Maternal events										
Events (any) per person-month	–	–	0.15 (0.19)	–	–	0.15 (0.17)	–	–	0.15 (0.24)	0.790
Infectious events per person-month	–	–	0.05 (0.08)	–	–	0.04 (0.07)	–	–	0.05 (0.10)	0.413
URTI	–	–	0.01 (0.03)	–	–	0.01 (0.03)	–	–	0.01 (0.03)	0.274
LRTI	–	–	0.02 (0.05)	–	–	0.02 (0.04)	–	–	0.02 (0.05)	0.804
Malaria	–	–	0.001 (0.02)	–	–	0 (0)	–	–	0.01 (0.05)	0.321
Gastroenteritis	–	–	0.01 (0.04)	–	–	0.01 (0.04)	–	–	0.01 (0.03)	0.508
Candida	–	–	0.001 (0.01)	–	–	0.01 (0.01)	–	–	0.001 (0.01)	0.525
Sepsis	–	–	0.005 (0.02)	–	–	0.003 (0.01)	–	–	0.01 (0.04)	0.292
Other events per person-month	–	–	0.10 (0.16)	–	–	0.10 (0.14)	–	–	0.10 (0.22)	0.937
Infant events										
Events (any) per person-month	–	–	0.20 (0.21)	–	–	0.22 (0.20)	–	–	0.16 (0.23)	0.027
Infectious events per person-month	–	–	0.15 (0.17)	–	–	0.16 (0.16)	–	–	0.12 (0.19)	0.111
URTI	–	–	0.03 (0.06)	–	–	0.03 (0.06)	–	–	0.03 (0.08)	0.672
LRTI	–	–	0.08 (0.11)	–	–	0.09 (0.11)	–	–	0.05 (0.11)	0.027
Malaria	–	–	0.001 (0.01)	–	–	0.001 (0.01)	–	–	0.002 (0.01)	0.397
Gastroenteritis	–	–	0.03 (0.06)	–	–	0.02 (0.05)	–	–	0.03 (0.07)	0.766
Candida	–	–	0.001 (0.01)	–	–	0.001 (0.01)	–	–	0.001 (0.01)	0.977
Sepsis	–	–	0.007 (0.03)	–	–	0.008 (0.03)	–	–	0.006 (0.02)	0.563
Other events per person-month	–	–	0.05 (0.08)	–	–	0.06 (0.09)	–	–	0.03 (0.07)	0.015
Maternal Hb, month 6 (g/dL)	n = 67	–	11.9 (1.5)	n = 55	–	11.8 (1.4)	n = 12	–	12.8 (1.8)	0.024
Maternal Hb, month 12 (g/dL)	n = 68	–	12.5 (1.6)	n = 56	–	12.4 (1.7)	n = 12	–	13.0 (1.0)	0.183
Infant Hb, month 12 (g/dL)	n = 49	–	10.5 (1.2)	n = 40	–	10.5 (1.1)	n = 9	–	10.5 (1.4)	0.999

Hb = hemoglobin; HEU = HIV-exposed, uninfected; HUU = HIV-unexposed, uninfected; IQR = interquartile range (between 25 and 75 percentile); LRTI = lower respiratory tract infection; URTI = upper respiratory tract infection.
* At least 330 days of follow-up.

of any type (105/157 [66.9%] versus 32/70 [45.7%] in HIV-negative women; P = 0.003) and noninfectious events (84/157 [53.5%] versus 24/70 [34.3%]; P = 0.007), whereas the proportion of women who experienced infectious events was similar in the two groups (57/157 [36.3%] in HIV-positive women versus 22/70 [31.4%] in HIV-negative women; P = 0.476).

To adjust for the significant difference in follow-up between the two groups, events were adjusted for duration of follow-up, analyzing the rates of any event, infectious events, and noninfectious events per person-month of follow-up. The overall rate in the entire group was 0.15 events per person-month. No differences between HIV-positive and HIV-negative women were observed in all the rates considered (Table 2).

No infant mortality was observed during follow-up. In infants, a total of 524 events were observed during the entire study, of whom 377 were infectious (five malaria, 78 URTI, 199 LRTI, 71 gastroenteritis, three candidiasis, 21 sepsis) and 147 noninfectious, mostly represented by skin rash/dermatitis (n = 84), conjunctivitis (n = 25), fever (n = 9), and otitis/otalgia (n = 7). Noninfectious events included one case of hypospadia, two cases of inguinal hernia (both in newborns at term), and one case of intussusception, all of which occurred in HEU infants.

HEU were significantly more likely to experience any event (124/157 [79.0%] versus 34/70 [48.6%]; P < 0.001), infectious events (110/157 [70.1%] versus 31/70 [44.3%]; P < 0.001), and noninfectious events (71/157 [45.2%] versus 17/70 [24.3%]; P = 0.003). Most of these differences were confirmed after adjusting for follow-up time: the overall event rate in the entire group of infants was 0.20 events per person-month,

with HEU showing compared with HUU a higher rate of any event (0.22 versus 0.16 events/person-month; P = 0.027), LRTI (0.09 versus 0.05 events/person-month; P = 0.027) and of noninfectious events (0.06 versus 0.03 events/person-month; P = 0.015). Infectious events were also more common in HEU compared with HUU (0.16 versus 0.12 events per person-month), but this difference did not achieve statistical significance (P = 0.111).

Maternal hemoglobin levels were almost 1 g lower in HIV-positive women at 6 months postpartum (11.8 versus 12.8 g/dL in HIV-negative women; P = 0.024) but similar at 12 months (12.4 versus 13.0 g/dL; P = 0.183). Infant hemoglobin values at 12 months were similar in the HEU and HEU groups (10.5 g/dL in both; P = 0.999)

Fifty-one women (the 12 on TDF/3TC/DTG, 27 on TDF/3TC/EFV, and 12 on other non–dolutegravir-based regimens) maintained their baseline regimens until last follow-up visit without toxicity or failure. Among the remaining 106 women who were on other regimens at baseline, 105 were switched to TDF/3TC/DTG according to national Malawi treatment transition guidelines, and one was switched at month 9 from TDF/3TC/EFV to zidovudine, lamivudine, atazanavir, and ritonavir because of treatment failure (last HIV-RNA viral load available: 20,950 copies/mL). No other cases of treatment failure were observed.

Infant growth. Data on infant growth up to 12 months are reported in Table 3. At 6 weeks, compared with HUU, HEU had a significantly lower BMI and BMIZ and a significantly lower WLZ. No significant differences were observed between the two groups in all the anthropometric measures collected at 6 and 12 months and in all growth indexes (weight

TABLE 3
Infant anthropometric measures and infant growth at 6 weeks, 6 months and 12 months

Anthropometric measures	6 weeks (n = HEU 142, HUU 50)			6 months (n = HEU 115, HUU 27)			12 months (n = HEU 120, HUU 24)		
	HEU	HUU	P	HEU	HUU	P	HEU	HUU	P
Infant length (cm)	53.9 (3.00)	53.4 (2.56)	0.316	65.3 (3.09)	64.2 (2.42)	0.080	72.2 (3.90)	71.6 (2.64)	0.481
Infant weight (kg)	4.78 (0.84)	4.96 (0.76)	0.166	7.80 (1.16)	7.72 (1.06)	0.747	9.25 (1.49)	9.11 (1.15)	0.669
BMI (kg/m^2)	16.3 (2.24)	17.4 (2.57)	0.006	18.3 (2.32)	18.8 (2.14)	0.236	17.6 (2.22)	17.7 (1.82)	0.842
BMI Z-score	0.69 (1.36)	1.31 (1.70)	0.010	0.64 (1.47)	1.07 (1.29)	0.167	0.60 (1.41)	0.78 (1.20)	0.569
Weight for age Z-score	0.03 (1.16)	0.31 (1.29)	0.150	−0.04 (1.23)	0.08 (1.19)	0.611	−0.22 (1.37)	−0.15 (1.14)	0.805
Length for age Z-score	−0.81 (1.40)	−1.05 (1.50)	0.298	−0.88 (1.40)	−1.12 (1.06)	0.398	−1.14 (1.30)	−1.24 (1.05)	0.733
Weight for length Z-score	1.06 (1.50)	1.94 (1.58)	0.001	0.78 (1.47)	1.19 (1.26)	0.185	0.49 (1.45)	0.60 (1.19)	0.733
Weight and length gain									
Weight gain between 6 weeks and 6 months (kg) (n = HEU 108, HUU 21)	2.99 (0.90)	2.99 (0.95)	0.998	—	—	—	—	—	—
Weight gain between 6 months and 12 months (kg) (n = HEU 100, HUU 16)	1.57 (0.90)	1.32 (0.72)	0.302	—	—	—	—	—	—
Weight gain between 6 weeks and 12 months (kg) (n = HEU 108, HUU 21)	4.58 (1.26)	4.14 (1.16)	0.141	—	—	—	—	—	—
Length growth between 6 weeks and 6 months (cm) (n = HEU 114, HUU 20)	11.4 (2.26)	11.2 (2.24)	0.690	—	—	—	—	—	—
Length growth between 6 months and 12 months (cm) (n = HEU 94, HUU 16)	7.40 (2.54)	7.75 (2.74)	0.620	—	—	—	—	—	—
Length growth between 6 weeks and 12 months (cm) (n = HEU 111, HUU 20)	18.4 (3.17)	19.2 (2.12)	0.231	—	—	—	—	—	—

HEU = HIV-exposed, uninfected; HUU = HIV-unexposed, uninfected.
All values are means (SD), compared with the Student's t-test for independent samples.

and length gain) evaluated between 6 weeks and 12 months (Table 3).

The analyses of stunting, underweight, and wasting at 6 weeks, 6 months, and 12 months by infant HIV exposure status are reported in Table 4. No significant differences were observed between HEU and HEU for all comparisons. Stunting was more common at all time points (overall 19.7% at 6 weeks, 19.6% at 6 months, and 22.9% at 12 months), compared with underweight (5.2% at 6 weeks, 2.7% at 6 months, and 7.4% at 12 months) and to wasting (2.1% at 6 weeks, 3.5% at 6 months, 4.1% at 12 months). Severe stunting (LAZ below –3), severe underweight (WAZ below –3), and severe wasting (WLZ below –3) were even less common and not significantly different between the two groups of HEU and HUU at any of the time points considered (Table 4).

Because of the relevance of stunting and to its common occurrence at all timepoints, we evaluated its potential determinants. In univariate analyses, stunting at any timepoint (6 weeks, 6 months, or 12 months) was associated at significance levels < 0.15 with rural or periurban residence ($P = 0.002$), lower maternal BMI ($P = 0.005$), lower education level ($P = 0.085$), and number of children in household ($P = 0.127$), and not associated (all P values > 0.2) with electricity or water in the house; duration of travel to the health center; maternal age; or hemoglobin levels, marital, and working status. The results of the multivariable logistic regression model that included all the significant variables reported above ($P < 0.15$) plus HEU/HUU infant status are shown in Table 5. The variables that remained associated with a significantly increased risk of stunting were rural or periurban residence (adjusted odds ratio [AOR]: 3.445, 95% confidence interval [CI]: 1.390–8.537, $P = 0.008$) and lower BMI (AOR per each additional BMI unit: 0.890, 95% CI: 0.805–0.985; $P = 0.024$), with an association of borderline significance between infant stunting and lower maternal education level (AOR for no or primary education versus secondary or higher education: 1.881, 95% CI: 0.964–3.671; $P = 0.064$). HEU/HUU status was not associated with stunting ($P = 0.621$; Table 5).

DISCUSSION

Different studies conducted in Africa have shown that HEU children may experience worse outcomes than HUU children in terms of mortality, hospitalization, and morbidity.[3,9,10,27–33] Most of this evidence was collected before widespread use of maternal lifelong ART and prolonged breastfeeding, however—two factors that play a major role in determining mortality in this population.[5,6,8,34] In some studies that adjusted for confounders, no differences were found.[5,35]

To contribute to this topic with recent data, collected in the current widespread option B+ scenario in which all expectant mothers living with HIV receive treatment of life regardless of their CD4 count, we assessed two parallel cohorts of mother–infant pairs with different HIV maternal status.

The two maternal cohorts were well balanced, with the only significant differences between the two groups observed for age and area of residence: compared with HIV-negative women, HIV-positive women were older, more commonly

TABLE 4
Stunting/severe stunting, underweight/severe underweight, and wasting/severe wasting at 6 weeks, 6 months and 12 months, by infant HIV exposure status

Time of assessment	Stunting (LAZ less than –2)					Severe stunting (LAZ less than –3)				
	n/N	%	OR	95% CI	P	n/N	%	OR	95% CI	P
6 weeks										
HEU	25/143	17.5	0.603	0.281–1.296	0.195	9/143	6.3	1.052	0.273–4.052	0.941
HUU	13/50	26.0				3/50	6.2			
6 months										
HEU	23/116	19.8	1.088	0.372–3.182	0.877	7/116	6.0	1.670	0.197–14.171	0.638
HUU	5/27	19.6				1/27	3.7			
12 months										
HEU	27/120	22.5	0.871	0.315–2.412	0.790	8/120	6.7	1.643	0.196–13.779	0.647
HUU	6/24	25.0				1/24	4.2			
	Underweight (WAZ less than –2)					Severe underweight (WAZ less than –3)				
6 weeks										
HEU	7/143	4.9	0.806	0.200–3.246	0.762	2/143	1.4	0.695	0.062–7.835	0.768
HUU	3/50	6.0				1/50	2.0			
6 months										
HEU	4/118	3.4	NC	NC	0.998	1/118	0.8	NC	NC	0.998
HUU	0/28	0.0				0/28	0.0			
12 months										
HEU	10/124	8.1	2.018	0.246–16.540	0.513	2/124	1.6	NC	NC	0.998
HUU	1/24	4.2				0/24	0.0			
	Wasting (WLZ less than –2)					Severe wasting (WLZ less than –3)				
6 weeks										
HEU	4/139	2.9	NC	NC	0.998	1/139	0.7	NC	NC	0.998
HUU	0/48	0.0				0/48	0.0			
6 months										
HEU	5/115	4.3	NC	NC	0.998	2/115	1.7	NC	NC	0.998
HUU	0/27	0.0				0/27	0.0			
12 months										
HEU	5/122	4.1	0.983	0.110-8.810	0.988	0/122	0.0	NC	NC	NC
HUU	1/24	4.2				0/24	0.0			

CI = confidence interval; HEU = HIV-exposed uninfected infants; HUU = HIV-unexposed uninfected infants; LAZ less than −2 = length for age Z-score more than 2 SD below the WHO population median; LAZ less than −3 = length for age Z-score more than 3 SD below the WHO population median; NC = not calculable; OR = odds ratio; WLZ less than −2 = weight for length Z-score more than 2 SD below the WHO population median; WLZ less than −3 = weight for length Z-score more than three SD below WHO population median; WAZ less than −2 = weight for age Z-score more than 2 SD below the WHO population median; WAZ less than −3 = weight for age Z-score more than 3 SD below the WHO population median.

lived in urban areas, and more commonly followed at the urban clinical site of Blantyre. We accounted for significant demographic differences in the multivariable analyses that assessed determinants of stunting.

Roughly half of HIV-negative women completed follow-up compared with 90% of HIV-positive women, who consequently had a 3-month longer mean follow-up. Because of this important difference, we adjusted event occurrence by follow-up time, analyzing event rate per month of follow-up. The reasons for worse follow-up attendance among HIV-negative women are uncertain. More than half of the study was conducted during the COVID-19 pandemic, which greatly affected visit attendance due to restrictions in circulation and possible fear of contracting SARS-CoV-2 infection. In this background, HIV-positive women may have attended more regularly due to their necessity to attend visits and obtain drug supplies for maintaining continuous antiretroviral therapy.

No maternal mortality was observed in the two cohorts. Low mortality in women receiving ART is well described, and the present data confirm previous findings.[36,37] Maternal events during follow-up were infrequent, with virtually identical rates in the two groups of HIV-positive and HIV-negative women for events of any type, infectious events, and noninfectious events. HIV-positive women, however, had significantly lower mean hemoglobin levels at 6 months (11.8 versus 12.8 g/dL, respectively). Similar differences have already been described.[38] We showed that this gap was partially reduced at 12 months, however, when the difference between the two groups was less pronounced (12.4 versus 13.0 g/dL; $P = 0.183$). These data suggest that HIV-positive women are particularly at risk of developing anemia during the first 6 months postpartum.

TABLE 5
Multivariable logistic regression analysis of stunting (LAZ less than –2) at any timepoint (6 weeks, 6 months, or 12 months)

	AOR	AOR 95% CI	P
Rural or semirural residence	3.445	1.390–8.537	0.008
Maternal BMI at month 1 (per additional unit)	0.890	0.805–0.985	0.024
No or primary school education level	1.881	0.964–3.671	0.064
Number of children in the household (per additional child)	0.874	0.678–1.127	0.299
HEU status	1.211	0.568–2.581	0.621

AOR = adjusted odds ratio; BMI = body mass index; CI = confidence interval; HEU = HIV exposed uninfected infant.

Micronutrients and iron supplementations during breastfeeding might be effective.

No infant mortality was observed during follow-up in the two infant cohorts. However, analysis of infant events during follow-up showed some significant differences between infants with different HIV exposure status. HEU infants had a significantly higher rate of events of any type; a slightly, nonsignificant higher rate of infectious events; and a significantly higher rate of LRTI and of other (noninfectious) events, mostly represented by rash or dermatitis and conjunctivitis. HEU and HUU infants had overlapping hemoglobin levels at 12 months.

The increased risk of LRTI in HEU infants is consistent with other observations that reported LRTI as the leading infections causing hospitalization and death in HEU, alone or with gastroenteritis.[8,9,33,39–41] We did not observe any differences between the two groups in rates of URTI, malaria, gastroenteritis, Candida infection, and sepsis, which occurred less frequently. We were also unable to define the etiological agents of the LRTIs, particularly with respect to the potential role of invasive pneumococcal disease described by others,[33] but in our study, infants received pneumococcal vaccination at 6, 10, and 14 weeks.[21] The causes for the increased susceptibility of HEU to LRTI are uncertain. Decreased transplacental transfer of protective maternal antibodies[42] and alterations in immune response to vaccinal antigens have been described in HEU infants,[43] but it is unknown to what extent this may correlate with protection.

HEU infants also had a higher rate of other events, mostly represented by rash/dermatitis and conjunctivitis. We were unable to characterize these events more precisely, which might represent different conditions, including common exanthematous viral diseases, atopic dermatitis, and minor skin or ocular infections.

The assessment of infant growth showed a transient lower BMI and BMI Z-score in HEU infants only at 6 weeks. This gap progressively decreased during follow-up, and no further differences between the two groups were observed in anthropometric measures at 6 and 12 months in weight gain and length growth during follow-up, nor in the rate of stunting, underweight, and wasting at 6 weeks, 6 months, and 12 months.

These data are relevant because they indicate that in the current scenario of universal ART coverage, HEU infants, except for a transient postbirth gap in BMI, can expect similar growth compared with HUU, with no differences in anthropometric measures and in occurrence of underweight, stunting and wasting. Almost all previous studies that had showed lower WAZ, LAZ or increased rates of stunting in HEU were conducted before 2016.[11–16,41,44] It is therefore likely that the universal access to lifelong antiretroviral therapy, together with effective PMTCT programs, have determined better maternal conditions that translate to better infant growth. This assumption is indirectly supported by studies that have indicated maternal BMI and/or social factors as major determinants of impaired infant growth.[7,13,45] Consistent with these findings, we showed in a multivariable analysis that stunting had no association with HEU status but was significantly associated with residence, maternal BMI, and (to a lesser extent) maternal education level. Stunting was frequent in both groups and more common than underweight or wasting, confirming other observations.[44]

The main limitation of our study was the high rate of loss to follow-up among HIV-negative women and their infants, a finding that was previously described.[2] Despite this limitation, the study maintained sufficient power to detect significant differences between groups and may represent a basis for larger studies that may validate and expand the findings observed. Another study limitation is the lack of some laboratory and instrumental measures. Our evaluation of the determinants of stunting was based only on demographic and clinical parameters. Accurate dating of pregnancy with ultrasonography was not possible, and the date of last menstrual period reported by the women was not usable as it was often unknown or unreliable. This precluded a valid assessment of intrauterine growth, preterm deliveries, and small-for-gestational-age infants. We were also unable to measure laboratory indexes potentially related to intrauterine growth that might differ according to maternal HIV status. Some data showed lower insulin growth factor-1 levels in HEU compared with HUU, possibly driven by HIV-induced maternal chronic inflammation.[46] In the study setting, an assessment of the biochemical correlates of nutritional status and inflammation was unfortunately not possible.

This study provides comparative data for clinical events and infant growth in two parallel cohorts of mothers and infants with different HIV status/exposure, simultaneously followed in the same settings, in recent times, and in a background of dolutegravir-based regimens for HIV treatment. In this context, intrauterine exposure to HIV was associated with some additional morbidity during the first year of life, represented by LRTI. Although such morbidity was not severe, further research is necessary to understand to what extent it can be prevented. Although no major differences were observed between HEU and HUU infants in growth and nutritional status, the common occurrence of stunting and its association with maternal clinical and demographic conditions prompt the implementation of interventions aimed at improving maternal health and social conditions.

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