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Measles Immunity at 4.5 Years of Age Following Vaccination at 9 and 15–18 Months of Age Among Human Immunodeficiency Virus (HIV)–infected, HIV-exposed–uninfected, and HIV-unexposed Children

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Background. Human immunodeficiency virus (HIV)–infected and HIV-exposed–uninfected (HEU) children may be at increased risk of measles infection due to waning of immunity following vaccination. We evaluated persistence of antibodies to measles vaccination at 4.5 years of age in HIV-unexposed, HEU, and HIV-infected children with CD4+ ≥25% previously randomized to immediate antiretroviral therapy (ART) interrupted at 12 months (HIV/Immed-ART-12), 24 months (HIV/Immed-ART-24), or when clinically/immunologically indicated (HIV/Def-ART). The HIV/Def-ART group initiated ART by median 5.8 (interquartile range, 4.4–10.3) months of age.

Methods. In this study, HIV-unexposed (n = 95), HEU (n = 84), HIV/Immed-ART-12 (n = 70), HIV/Immed-ART-24 (n = 70), and HIV/Def-ART (n = 62) children were scheduled to receive measles vaccination at age 9 and 15–18 months. Antimeasles serum immunoglobulin G titers were quantified using enzyme-linked immunosorbent assay at 4.5 years.

Results. Compared with HIV-unexposed children (2860 mIU/mL), measles antibody geometric mean titers (GMTs) were significantly lower in both HIV/Immed-ART-12 (571; $P < .001$) and HIV/Immed-ART-24 (1136; $P < .001$) but similar in the HIV/Def-ART (2777) and HEU (3242) groups. Furthermore, compared with HIV-unexposed, antibody titers ≥330 mIU/mL (ie, presumed serocorrelate for protection; 99%) were also significantly lower in HIV/Immed-ART-12 (70%; $P < .001$) and HIV/Immed-ART-24 (83%; $P < .001$) but similar in the HIV/Def-ART (90%) and HEU (98%) groups.

Conclusions. HIV-infected children in whom ART was interrupted at either 12 or 24 months had lower GMTs and lower proportions with seroprotective titers than HIV-unexposed children, indicating a potential downside of ART treatment interruption.

Clinical Trials Registration. NCT00099658 and NCT00102960.

Keywords. antibody response; measles vaccine; HIV; HIV exposure; persistence.

In 2015, measles infection contributed to 1.2% (134 200 deaths) of global mortality in children aged <5 years [1]. Despite safe and effective vaccines [2], sporadic outbreaks of measles still persist [3] due to low vaccine coverage, reduced maternal measles antibody transfer to infants born to vaccinated women compared with those with naturally acquired immunity, and pockets of susceptible individuals with suboptimal immune responses to vaccination [4, 5].

Following measles vaccination, human immunodeficiency virus (HIV)–infected children maintain seroprotective titers for a shorter duration than HIV-uninfected children [6–9]. A meta-analysis [7] of 5 studies estimated that 68% (95% confidence interval [CI], 45%–88%) of HIV-infected primary responders had seroprotective antibody titers 2 years after their last measles vaccine and 40% (95% CI, 10%–73%) after 5 years, generally in the absence of combination antiretroviral therapy (ART) [10].

Increased ART coverage has improved survival of HIV-infected children, potentially creating a cohort of measles-susceptible children due to quicker waning of antibodies over time [11]. Two studies have been published on measles seroresponses in HIV-infected children receiving early ART initiation, as currently recommended by the World Health Organization (WHO) [12]. Pensieroso et al reported that early ART-treated HIV-infected children generated and preserved measles-specific memory B cells comparable to healthy controls

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[13]. However, Succi et al observed no difference in measles seropositivity at 4 years of age between children on ART initiated <12 months age, ≥12 months of age, or no ART [14]. Although early initiation of ART in HIV-infected infants is now recommended, lifelong continuous treatment may be problematic due to long-term toxicity, risk of ART resistance, waning adherence, and resource constraints. Previous studies showed that early time-limited (interrupted) ART had improved clinical outcomes compared with deferred continuous ART [15].

Because of effective prevention of mother-to-child-transmission, a large proportion of children born to HIV-infected mothers are HIV exposed but uninfected (HEU) [16]. These children may have suboptimal immune response to vaccination due to intrauterine exposure to HIV and/or maternal ART [17–21]. HEU infants have reduced CD4+ and CD8+ cell counts, impaired T-cell maturation, and both hypo- and hyperresponsiveness upon T-cell activation [22–24]. We previously reported that the proportion with seroprotective measles antibody titers at approximately 9 months post-measles booster vaccination was lower in HEU (79.6%) than HIV-unexposed children (94.3%) [25]. In contrast, other studies have reported similar measles antibody persistence between HEU and HIV-unexposed children up to 2 years of age [8, 26–30].

A recent systematic review highlighted the absence of published studies on long-term immunity to measles vaccination beyond 2 years of age in HEU and HIV-infected children, especially with early ART initiation [31].

In this study, we aimed to evaluate persistence of measles antibody titers at 4.5 years of age in HIV-unexposed, HEU, and HIV-infected children previously randomized to initiate ART when clinically/immunologically indicated or within 6–12 weeks of age, which was interrupted at 12 or 24 months.

METHODS

Study Population

This cohort study included HIV-infected children enrolled in a randomized open-label trial on timing of ART initiation (Children with HIV Early Antiretroviral [CHER] study) [32] and a parallel cohort of HEU and HIV-unexposed children [25, 33, 34]. The CHER study enrolled HIV-infected infants aged 6 to 12 weeks with CD4+ T-cell percentages ≥25% and randomized to initiate immediate ART followed by interruption at 12 months (HIV/Immed-ART-12) or 24 months (HIV/Immed-ART-24), or deferred ART until clinically or immunologically indicated (HIV/Def-ART). A convenience sample of HIV-infected children with CD4+ T-cell percentage <25% was included (HIV+/CD4+ <25%) who initiated ART at enrollment for 12 or 24 months followed by interruption. In parallel, children born to HIV-uninfected mothers (HIV-unexposed) and HIV-infected mothers who were themselves HIV-uninfected (HEU) were enrolled in this study.

Children included in this study were enrolled between April 2005 and June 2006. The Schwarz measles vaccine (Rouvax, Aventis, France) was administered at 38–42 weeks (9 months) and 64–76 weeks (15–18 months) of age. Participants received other childhood vaccines according to the public immunization program [25, 34]. The ART regimen consisted of zidovudine, lamivudine, and lopinavir-ritonavir. An interim analysis of the CHER trial showed greater risk of disease progression and death in the HIV/Def-ART group and thus recommended they be evaluated for ART initiation [32]. Children in the HIV/Def-ART group began ART at median age 5.8 months (interquartile range [IQR], 4.4–10.3 months); 73% had been initiated on ART before receiving the first measles vaccine and 88% before receiving the booster measles dose. Those in HIV/Immed-ART-12 and HIV/Immed-ART-24 groups were initiated on ART at a median age of 7.4 (IQR, 6.6–8.9) weeks.

Laboratory Methods

Blood samples were collected at 4.5 years (232–236 weeks) of age. After centrifugation, serum was aliquoted and stored at −20°C to −70°C. Measles-specific immunoglobulin G (IgG) antibodies were measured using an indirect enzyme-linked immunosorbent assay (Enzygnost, Dade Behring, Marburg, Germany). The assay included an internal reference for the quantitative assessment of measles IgG concentrations, adjusted according to the WHO International Reference Preparation (1964) [35]. Antibody titers were calculated using the α-method according to the manufacturer's instructions. Measles seropositivity was classified as IgG titers ≥150 mIU/mL (optical density [OD], 0.1–0.2) and seroprotection as titers ≥330 mIU/mL (OD >0.2) as per manufacturer's guidelines, which has been supported by other studies [36, 37]. All negative (<150 mIU/mL; OD <0.1) and equivocal (150–329 mIU/mL) samples were analyzed in duplicate. Seronegative samples were assigned a titer half the value of the assay's detection limit (ie, 75 mIU/mL).

Statistical Analyses

Geometric mean titers (GMTs) were calculated following $\log_{10}$ transformation of antibody titers and then compared between groups using multivariable linear regression, considering age, sex, race, study center, and CD4+ T-cell percentage at the 9-month measles dose as covariates. Proportions of children who met seropositivity and seroprotection cutoffs were compared between groups using multivariable logistic regression, adjusted for the aforementioned covariates.

Weight-for-height, weight-for-age, and height-for-age *z* scores were calculated using WHO child growth references [38]. Stunting was defined as height-for-age *z* score ≤2 standard deviations (SD) from the WHO reference population mean, wasting as weight-for-height score of ≤2 SD below the mean, and underweight as weight-for-age *z* score ≤2 SD below the mean.

Logistic regression was used to explore the association between long-term seroprotective antibody titers and HIV status, ART initiation strategy, sex, race, age, time interval between vaccination and blood collection, and nutritional status at the primary measles dose by reporting adjusted odds ratios (aORs) and 95% CIs. In HIV-infected children, we further analyzed the effect of ART (at time of primary and booster measles doses, immunogenicity visit) and CD4+ T-cell percentage (at enrollment and primary measles dose) on the proportion of participants with seroprotective antibody titers. Variables with P values ≤ .15 in univariate regression were included in multivariable regression models. HIV-unexposed children were used as the reference group. Participants were included in the analyses if they received 2 doses of measles vaccination and had an immunogenicity visit with serum collection around 4.5 years of age. Unadjusted P values ≤ .05 and Bonferroni adjusted P values ≤ .007, taking multiple comparisons into consideration, were considered statistically significant. All tests were 2 sided. Data were analyzed using Stata version 13 (Stata Corporation, College Station, TX).

Ethics

The Human Research Ethics Committee of the University of the Witwatersrand approved this substudy (M170391). The parent trials were approved by ethics committees of the University of the Witwatersrand and the Stellenbosch University, Medicine Control Council (South Africa), and the Division of AIDS of the National Institutes of Health. Written informed consent was obtained from the parent(s) of participants prior to study entry, including approval to analyze immune responses to other vaccines.

RESULTS

Of 578 children enrolled, samples were unavailable for 141 (24%) participants at 4.5 years of age, as detailed in Figure 1, and included high infant mortality rates in HIV/Def-ART (19%; n = 20), HIV/Immed-ART-12 (10%; n = 11), and HIV-Immed-ART-24 (8%; n = 8) groups [32]. Of the 437 children who received 2 doses of measles vaccine, 388 (89%) had serum samples for analysis at median age of 4.4 years: 95 HIV-unexposed, 84 HEU, 70 HIV/Immed-ART-12, 70 HIV/Immed-ART-24, 62 HIV/Def-ART, and 7 HIV-infected with CD4+ <25% (Table 1). Baseline characteristics of children included in the current analyses were not significantly different from those who were excluded, except for deaths and those administered <2 doses of measles vaccine (Supplementary Table 1).

Overall, the median age at time of the primary measles dose was 9.0 months and at booster dose 15.4 months with a time interval of median 37.7 months between primary vaccination and the immunogenicity visit (Table 1). Differences in age at vaccination between groups were unlikely to be of clinical relevance. More children were of black-African descent in the HEU (95%), HIV/Immed-ART-12 (93%), HIV/Immed-ART-24 (96%), and HIV/Def-ART (98%) groups compared with HIV-unexposed children (80%). More HIV-infected children (HIV/Immed-ART-12, 31%; HIV/Def-ART, 45%) were stunted at the primary measles dose than HIV-unexposed (14%) and HEU (14%) children; however, nutritional status was similar by 4.5 years of age (Table 1).

Total number of HIV-infected children per group (re-)initiated on ART at the time of vaccinations and sample collection and duration of ART interruption are presented in Table 1 and Supplementary Figure 1. Mean CD4+ percentage and median CD4+ count were significantly different between HIV groups (Table 1).

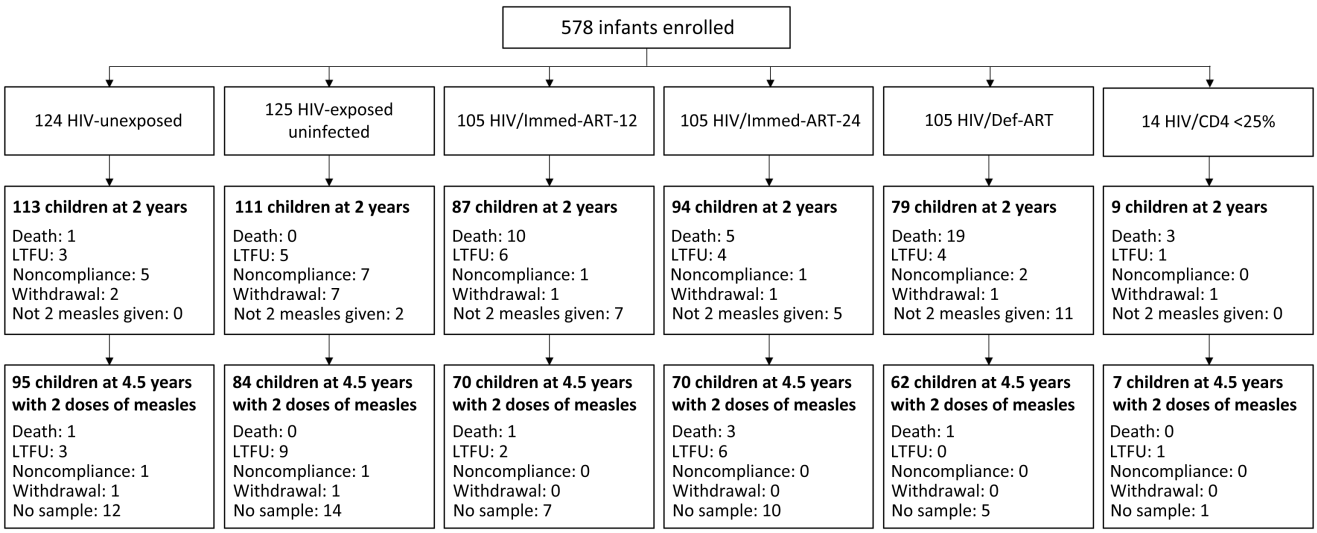

Figure 1. Study profile showing the study population from enrollment through the current analysis. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; HIV/Immed-ART-12, HIV-infected children receiving immediate ART until 12 months of age; HIV/Immed-ART-24, HIV-infected children receiving immediate ART until 24 months of age; HV/Def-ART, HIV-infected children on deferred ART until clinically or immunologically indicated; HIV/CD4+ <25%, convenience sample of HIV-infected children with CD4+ <25% at enrollment and immediate initiation on ART; LTFU, loss to follow-up.

Table 1. Demographics and Baseline Characteristics of Participants Included in the Immunogenicity Analysis

Characteristic	HIV-Unexposed (n = 95)	HEU (n = 84)	HIV/Immed-ART-12 (n = 70)	HIV/Immed-ART-24 (n = 70)	HIV/Def-ART (n = 62)	HIV/CD4+ <25% (n = 7)	Total (n = 388)
Male, n (%)	50 (53)	43 (51)	24 (34)	36 (51)	23 (37)	2 (29)	178 (46)
Black-African, n (%)	76 (80)[a,b,c,d]	80 (95)[a]	65 (93)[b]	67 (96)[c]	61 (98)[d]	6 (86)	355 (91)
Mixed ancestry, n (%)	19 (20)[a,b,c,d]	4 (5)[a]	5 (7)[b]	3 (4)[c]	1 (2)[d]	1 (14)	33 (9)
Age at primary measles dose, median months (IQR)	8.9 (8.8–9.0)[a,b,c,d]	9.0 (8.9–9.1)[a]	9.0 (8.8–9.2)[b]	9.1 (8.9–9.4)[c]	9.2 (8.9–9.5)[d]	9.5 (8.9–9.7)	9.0 (8.8–9.2)
Age at booster measles dose, median months (IQR)	15.2 (15.2–15.4)[a,b,c,d]	15.4 (15.3–15.6)[a,e]	15.5 (15.3–15.9)[b]	15.5 (15.3–15.7)[c]	15.7 (15.3–16.5)[d,e]	15.7 (15.2–15.9)	15.4 (15.2–15.7)
Age at immunogenicity visit, median years (IQR)	4.4 (4.4–4.5)	4.4 (4.4–4.5)	4.4 (4.4–4.5)	4.4 (4.4–4.5)	4.4 (4.4–4.5)	4.5 (4.5–4.6)	4.4 (4.4–4.5)
Interval from primary measles dose to immunogenicity visit, median months (IQR)	37.7 (37.7–38.2)[b,d]	37.7 (37.7–38.1)[e]	37.6 (36.9–38.1)[b]	37.7 (37.5–38.0)	37.7 (36.7–38.1)[d,e]	38.5 (38.4–38.7)	37.7 (37.6–38.1)
Stunting[f] at primary measles dose, n (%)	13 (14)[b,d]	12 (14)[e]	22 (31)[b]	13 (19)[h]	27 (45)[d,e,h]	3 (43)	90 (24)
Wasting[i] at primary measles dose, n (%)	3 (3)	3 (4)	3 (4)	0 (0)	1 (2)	0 (0)	10 (3)
Underweight[j] at primary measles dose, n (%)	8 (8)	3 (4)	8 (11)	4 (6)	8 (13)	0 (0)	31 (8)
Stunting at immunogenicity visit, n (%)	10 (11)	18 (21)	18 (26)	16 (23)	11 (18)	3 (43)	76 (20)
Wasting at immunogenicity visit, n (%)	1 (1)	1 (1)	0 (0)	0 (0)	1 (2)	0 (0)	3 (1)
Underweight at immunogenicity visit, n (%)	5 (5)	1 (1)	3 (4)	1 (1)	3 (5)	0 (0)	13 (3)
Enrollment CD4+ lymphocyte count, median cells/mL (IQR)	NA	NA	1980 (1695–2722)	2283 (1739–2924)	2612 (1771–3277)	1727 (963–2356)	2283 (1695–2982)
Enrollment CD4+ lymphocyte %, mean (±SD)	NA	NA	36.5 (8.3)	38.0 (8.9)	38.1 (7.8)	22.6 (4.3)	37.0 (8.7)
Primary measles dose CD4+ lymphocyte count, median cells/mL (IQR)	NA	NA	2104 (1579–2713)[k]	2149 (1604–2746)[h]	1518 (1207–2189)[h,k]	1495 (1209–2330)	1970 (1421–2583)
Primary measles dose CD4+ lymphocyte %, mean (±SD)	NA	NA	40.0 (9.3)[k]	39.1 (7.7)[h]	31.5 (6.8)[h,k]	32.0 (8.0)	36.9 (8.8)
Booster measles dose CD4+ lymphocyte count, median cells/mL (IQR)	NA	NA	1286 (1016–1746)[k,l]	1860 (1306–2220)[l]	1734 (1357–2277)[k]	1612 (900–1976)	1614 (1181–2131)
Booster measles dose CD4+ lymphocyte %, mean (±SD)	NA	NA	26.3 (7.1)[k,l]	34.2 (7.9)[l]	34.2 (8.4)[k]	29.7 (10.2)	31.4 (8.6)
Immunogenicity visit CD4+ lymphocyte count, median cells/mL (IQR)	NA	NA	1055 (723–1330)[k]	945 (715–1241)[h]	1202 (910–1524)[h,k]	No observations	1057 (779–1383)
Immunogenicity visit CD4+ lymphocyte %, mean (±SD)	NA	NA	31.7 (7.4)[k]	30.0 (7.4)[h]	36.6 (7.7)[h,k]	No observations	32.5 (7.9)
Total on ART at 9-month measles dose, n/N (%)	NA	NA	69/70 (99)[k]	70/70 (100)[h]	44/62 (71)[h,k]	7/7 (100)	190/209 (91)
Total on ART at 15–18-month measles dose, n/N (%)	NA	NA	21/70 (30)[k,l]	70/70 (100)[h,l]	53/62 (85)[h,k]	7/7 (100)	151/209 (72)

Table 1. Continued

Characteristic	HIV-Unexposed (n = 95)	HEU (n = 84)	HIV/Immed-ART-12 (n = 70)	HIV/Immed-ART-24 (n = 70)	HIV/Def-ART (n = 62)	HIV/CD4+ <25% (n = 7)	Total (n = 388)
Total on ART at immunogenicity visit, n/N (%)	NA	NA	50/70 (71)[k]	44/70 (63)[h]	58/62 (94)[h,k]	7/7 (100)	159/209 (76)
Interval from ART initiation to primary measles dose, median months (IQR)	NA	NA	7.4 (7.4; 7.5)[k]	7.4 (7.4; 7.4)[h]	3.7 (−1.3; 5.5)[h,k]	7.4 (7.4; 7.5)	7.4 (5.6; 7.4)
Duration of ART interruption, median months (IQR)	NA	NA	7.3 (3.2; 45.3)[k]	16.5 (3.9; 34.1)[h]	0 (0; 0)[h,k]	0 (0; 0)	3.9 (0; 21.4)

Five participants had missing data on nutritional status primary measles dose vaccination; 12 (HIV/Def-ART group) and 25 (HIV/Immed-ART groups) participants had missing data on CD4+ T cell count/percentage at the immunogenicity visit. *P* values were calculated using a Kruskal–Wallis test and adjusted for multiple comparisons.

Abbreviations: ART, antiretroviral therapy; CD4+ <25%, HIV-infected children with CD4+% <25% at enrollment who received immediate ART; HEU; HIV-exposed–uninfected children; HIV, human immunodeficiency virus; HIV/Immed-ART-12, HIV-infected children on immediate ART interrupted at 12 months; HIV/Immed-ART-24, HIV-infected children on immediate ART interrupted at 24 months; HIV/Def-ART, HIV-infected children on deferred ART; IQR, interquartile range; NA, not applicable; SD, standard deviation.

[a]Significant difference between HIV-unexposed and HEU.

[b]Significant difference between HIV-unexposed and HIV/Immed-ART-12.

[c]Significant difference between HIV-unexposed and HIV/Immed-ART-24.

[d]Significant difference between HIV-unexposed and HIV/Def-ART.

[e]Significant difference between HEU and HIV/Def-ART.

[f]Stunting: height-for-age *z* score ≤2 SD.

[g]Significant difference between HEU and HIV/Immed-ART-12.

[h]Significant difference between HIV/Immed-ART-24 and HIV/Def-ART.

[i]Wasting: weight-for-height score ≤2 SD.

[j]Underweight: weight-for-age *z* score ≤2 SD.

[k]Significant difference between HIV/Immed-ART-12 and HIV/Def-ART.

[l]Significant difference between HIV/Immed-ART-12 and HIV/Immed-ART-24.

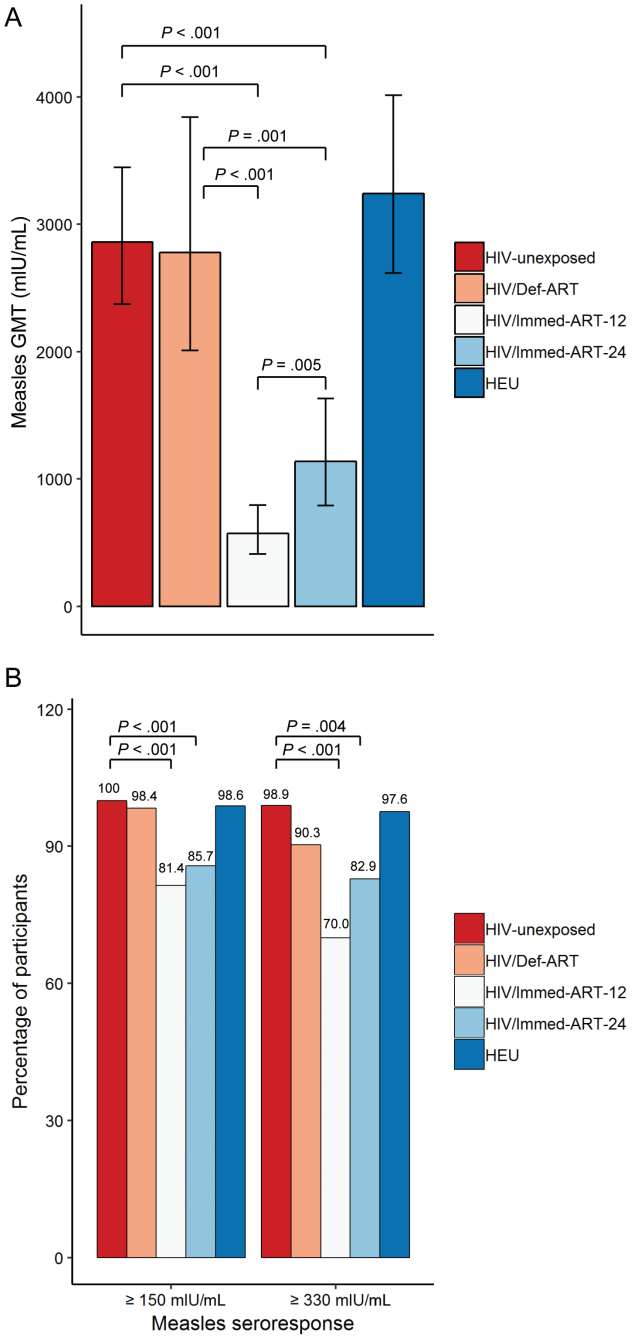

Figure 2. Measles antibody geometric mean titers and proportion of children with seropositive and seroprotective antibody levels at 4.5 years of age. *P* value deemed significant at ≤.007 after Bonferroni correction. *P* values were either calculated by linear or logistic regression and adjusted for age at the immunogenicity visit, sex, race, study center, and CD4+ cell percentage at the primary measles dose in HIV-infected children or by Fisher exact test. Abbreviations: ART, antiretroviral therapy; GMT, geometric mean titer; HEU, HIV-exposed uninfected; HIV, human immunodeficiency virus; HIV/Def-ART, HIV-infected children on deferred ART until clinically or immunologically indicated; HIV/Immed-ART-12, HIV-infected children receiving immediate ART until 12 months of age; HIV/Immed-ART-24, HIV-infected children receiving immediate ART until 24 months of age.

Persistence of Measles Antibodies at 4.5 Years of Age

GMTs were lower in HIV/Immed-ART-12 (571 mIU/mL) and HIV/Immed-ART-24 (1136 mIU/mL) children than in HIV-unexposed children (2860 mIU/mL; $P < .001$ for both comparisons). Also, GMTs were lower in the HIV/Immed-ART-12 and HIV/Immed-ART-24 groups than in the HIV/Def-ART children (2777 mIU/mL; $P < .001$ and $P = .001$, respectively) when adjusted for race, study center, age and CD4+ percentage at time of the primary measles dose. Furthermore, GMTs were significantly lower in HIV/Immed-ART-12 children compared with HIV/Immed-ART-24 children ($P = .005$; Figure 2A; Supplementary Table 2).

Measles seropositivity (≥150 mIU/mL) was present in all HIV-unexposed children and 98.4% of the HIV/Def-ART groups ($P = .395$). In contrast, fewer children in the HIV/Immed-ART-12 (81.4%; $P < .001$) and HIV/Immed-ART-24 (85.7%; $P < .001$) groups were seropositive than HIV-unexposed children (Figure 2B, Supplementary Table 2).

Similarly, the percentage of children with seroprotective titers (ie, ≥330 mIU/mL) was significantly lower in the HIV/Immed-ART-12 (70.0%; $P < .001$) and HIV/Immed-ART-24 (82.9%; $P = .004$) groups compared with HIV-unexposed children (99.0%). In the HIV/Def-ART group, 90.3% had seroprotective titers. Of 7 children with CD4+ T-cell <25% at enrollment, 85.7% were measles seropositive and 85.7% had seroprotective titers. There were no differences in GMTs, seropositivity, or percentage with seroprotective titers between the HEU and HIV-unexposed children (Figure 2B, Supplementary Table 2).

Exclusion of participants in the early therapy groups who did not interrupt ART for various reasons and proceeded on continuous ART (n = 3 in HIV/Immed-ART-12, n = 10 in HIV/Immed-ART-24 and n = 6 in CD4+<25% groups) did not significantly alter results (Supplementary Table 3).

Determinants of Long-term Seroprotection

We examined the association between long-term measles seroprotection and HIV status, timing of ART initiation, sex, race, age at vaccination, age at immunogenicity visit, and nutritional status at the primary measles dose among all children (n = 381) in univariate and multivariable logistic regression (Table 2). After controlling for timing of ART initiation, sex, race, age at vaccination, age at immunogenicity visit, and nutritional status, HIV/Immed-ART-12 (aOR, 0.03; 95% CI, 0.003–0.20), HIV/Immed-ART-24 (aOR, 0.05; 95% CI, 0.006–0.41), and HIV/Def-ART (aOR, 0.11; 95% CI, 0.01–0.90) children had a lower odds for seroprotective titers relative to HIV-unexposed children.

Among HIV-infected children (n = 202), we assessed the association of measles seroprotection with the aforementioned covariates, in addition to receipt of ART at the time of the primary or booster dose, ART at 4.5 year of age, and CD4+ T-cell percentage at enrollment or primary dose. In multivariable logistic regression, HIV-infected children who received ART at the time of the booster measles dose were 2.27 (95% CI, 1.02–5.05) more likely to have antibody titers ≥330 mIU/mL than those who did not receive ART. Similarly, ART at time of measuring antibody persistence (aOR, 3.07; 95% CI, 1.39–6.84)

Table 2. Association of Measles Seroprotection at 4.5 Years of Age With Human Immunodeficiency Virus Status, Sex, Age at Vaccination, Nutritional Status at Primary Measles Dose, Antiretroviral Therapy Regimen, and Immune Status

Characteristic	Nonseroprotected	Seroprotected	Univariate OR (95% CI) for Seroprotection[a]	*P* Value	Adjusted OR (95% CI) for Seroprotection[a]	*P* Value
All children (n = 381[b,c])	n = 42	n = 339	…	…	…	…
HIV status						
HIV unexposed	1/42 (2.4)	94/339 (27.7)	Ref.	…	Ref.	…
HIV exposed, uninfected	2/42 (4.8)	82/339 (24.2)	0.44 (0.04–4.90)	.501	0.44 (0.04–4.93)	.504
HIV/Immed-ART-12	21/42 (50.0)	49/339 (14.5)	0.02 (0.003–0.19)	<.001	0.03 (0.003–0.20)	<.001
HIV/Immed-ART-24	12/42 (28.6)	58/339 (17.1)	0.05 (0.007–0.41)	.005	0.05 (0.006–0.41)	.005
HIV/Def-ART	6/42 (14.3)	56/339 (16.5)	0.10 (0.01–0.85)	.035	0.11 (0.01–0.90)	.040
Sex						
Male	14/42 (33.3)	162/339 (47.8)	Ref.	…	Ref.	…
Female	28/42 (66.7)	177/339 (52.2)	0.55 (0.28–1.07)	.080	0.66 (0.32–1.36)	.262
Race						
Black	41/42 (97.6)	308/339 (90.9)	…	…	…	…
Mixed ancestry	1/42 (2.4)	31/339 (9.1)	NA	.169	NA	…
Age at primary measles dose (mo)	9.0 (8.8–9.1)	9.0 (8.8–9.2)	1.07 (0.49–2.36)	.859	NA	…
Age at booster measles dose (mo)	15.4 (15.2–15.8)	15.4 (15.2–15.7)	1.11 (0.76–1.63)	.588	NA	…
Age at immunogenicity visit (mo)	53.1 (52.9–53.5)	53.2 (52.9–53.7)	1.14 (0.72–1.82)	.581	NA	…
Interval from booster measles dose to immunogenicity visit (mo)	37.7 (37.5–37.9)	37.7 (37.5–38.1)	0.97 (0.78–1.21)	.812	NA	…
Stunting at primary measles dose						
No	32/41 (78.1)	257/335 (76.7)	Ref.	…	…	…
Yes	9/41 (22.0)	78/335 (23.3)	1.08 (0.49–2.36)	.849	NA	…
Wasting at primary measles dose						
No	41/41 (100.0)	325/335 (97.0)	…	…	…	…
Yes	0/41 (0.0)	10/335 (3.0)	NA	…	NA	…
Underweight at primary measles dose						
No	38/41 (92.7)	307/335 (91.6)	Ref.	…	…	…
Yes	3/41 (7.3)	28/335 (8.4)	1.16 (0.34–3.98)	.819	NA	…
HIV-infected children (n = 202)	n = 39	n = 163				
Sex						
Male	12/39 (30.8)	71/163 (43.6)	Ref.	…	Ref.	…
Female	27/39 (69.3)	92/163 (56.4)	0.58 (0.27–1.22)	.148	0.77 (0.34–1.72)	.522
Race						
Black	38/39 (97.4)	155/163 (95.1)	…	…	…	…
Mixed ancestry	1/39 (2.6)	8/163 (4.9)	NA	.531	NA	…
Age at primary measles dose (mo)	9.0 (8.8–9.1)	9.1 (8.9–9.4)	1.79 (0.73–4.36)	.202	NA	…
Age at booster measles dose (mo)	15.4 (15.2–15.8)	15.6 (15.3–15.9)	1.50 (0.81–2.76)	.196	NA	…
Age at immunogenicity visit (mo)	53.1 (52.9–53.5)	53.2 (52.7–53.8)	1.00 (0.60–1.68)	.999	NA	…
Interval from booster measles dose to immunogenicity visit (mo)	37.7 (37.5–37.9)	37.7 (36.8–38.1)	0.83 (0.59–1.16)	.272	NA	…
Stunting at primary measles dose[c]						
No	29/38 (76.3)	106/159 (66.7)	Ref.	…	…	…
Yes	9/38 (23.7)	53/159 (33.3)	1.61 (0.71–3.65)	.253	NA	…
Wasting at primary measles dose[c]						
No	38/38 (0.0)	155/159 (97.5)	Ref.	…	…	…
Yes	0/38 (0.0)	4/159 (2.5)	NA	…	NA	…
Underweight at primary measles dose[c]						
No	35/38 (92.1)	142/159 (89.3)	Ref.	…	…	…
Yes	3/38 (7.9)	17/159 (10.7)	1.40 (0.39–5.03)	.609	NA	…

Table 2. Continued

Characteristic	Nonseroprotected	Seroprotected	Univariate OR (95% CI) for Seroprotection[a]	*P* Value	Adjusted OR (95% CI) for Seroprotection[a]	*P* Value
ART at time of primary measles dose						
No	6/39 (15.4)	13/163 (7.98)	Ref.	…	Ref.	…
Yes	33/39 (84.6)	150/163 (92.0)	2.10 (0.74–5.92)	.162	2.16 (0.64–7.34)	.216
ART at time of booster measles dose						
No	20/39 (51.3)	38/163 (23.3)	Ref.	…	Ref.	…
Yes	19/39 (48.7)	125/163 (76.7)	3.46 (1.68–7.15)	.001	2.27 (1.02–5.05)	.044
ART at immunogenicity visit						
No	19/39 (48.7)	31/163 (19.0)	Ref.	…	Ref.	…
Yes	20/39 (51.3)	132/163 (81.0)	4.05 (1.93–8.48)	<.001	3.07 (1.39–6.84)	.006
Enrollment CD4+ T lymphocyte %	37.2 (31.4–43.3)	36.4 (31.8–42.4)	1.00 (0.96–1.04)	.942	NA	…
Primary measles dose CD4+ T lymphocyte %	39.6 (32.6–47.0)	36.7 (30.5–42.2)	0.96 (0.93–1.00)	.071	0.98 (0.93–1.03)	.396

Data are proportion of patients (%) or median (IQR).

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HIV/Immed-ART-12, HIV-infected children on immediate ART interrupted at 12 months; HIV/Immed-ART-24, HIV-infected children on immediate ART interrupted at 24 months; HIV/Def-ART, HIV-infected children on deferred ART; NA, not applicable; OR, odds ratio; Ref., reference group.

[a]Seroprotection was defined as an immunoglobulin G titer of ≥330 mIU/mL.

[b]Seven HIV-infected children with CD4+ <25% at enrollment were excluded from analyses.

[c]Five participants had missing information on nutritional status at the primary measles dose.

was associated with higher likelihood of seroprotective titers ≥330 mIU/mL, whereas this was not associated with CD4+ percentage at enrollment or at time of the primary vaccine dose (Table 2).

DISCUSSION

The results from this study underscore a potential downside of ART interruption in HIV-infected infants who initiated ART during early infancy, indicating greater waning of immunity against measles infection by 4.5 years of age than in HIV-unexposed children. Furthermore, our study dispelled earlier concerns of HEU also being predisposed to greater waning of immunity, as suggested by the previous observation in the same cohort of children 9 months after the booster dose of measles vaccine [25]. Notably, children in the HIV/Def-ART group, the majority (88%) of whom were on continuous ART by the time of their booster dose of measles vaccine, had measles immunity that was similar to that of HIV-unexposed children.

The attenuated antibody response in HIV/Immed-ART children compared with that in HIV/Def-ART children may be explained by the lower number of children on ART at the time of the immunogenicity visit in HIV/Immed-ART groups and the lower number on ART at booster vaccination in HIV/Immed-ART-12 children. These results are in line with our previous findings at 2 years of age, showing greater waning of immunity in children with interrupted ART [25]. Immune-cell activation during ART interruption may cause memory B cells to be drawn into effector pathways, resulting in depletion of memory B cells [39]. HIV/Immed-ART-12 children compared with HIV/Immed-ART-24 children had significantly lower GMTs. This may also be explained by fewer children in the HIV/Immed-ART-12 group on ART at the time of booster vaccination compared with HIV/Immed-ART-24.

The HIV/Def-ART group, who initiated continuous ART after the CHER interim analysis in June 2007, were less immunosuppressed, and a significantly higher proportion were on ART at the time of booster vaccination and immunogenicity visit compared with the HIV/Immed-ART group. The HIV/Def-ART group, however, might have been selectively biased by representing children with slower HIV progression within the group, as there was a higher mortality rate in these children (16%) compared with the HIV/Immed-ART children (4%) after a median follow-up of 40 weeks [32]. Nevertheless, our study does represent the survivors initially randomized to this group and suggests that ART should be initiated prior to measles vaccine immunization.

Two other studies have evaluated long-term measles antibody persistence in a much smaller number of HIV-infected children initiated on ART within the first year of life and reported results similar to ours. These included a Latin American cohort study in which seropositive titers (≥120 mIU/mL) were present in 87% of children at 4 years of age (n = 38) [14] and an Italian cross-sectional study in which 82% of children had seroprotective titers at 7 years (n = 13) of age [13]. The former, however, did not find a significant relation between the timing of ART initiation and measles serology [14]. Of note, no studies in children evaluated the effect of systematically assigned early ART on long-term measles antibodies and the consequences of interrupting ART.

The CHER study hypothesized that if children are initiated on early ART close to primary infection, disease progression

could be prevented and children could be allowed a subsequent period off ART [15]. In CHER, HIV-infected children on early ART in whom ART was interrupted had a better clinical outcome than those on deferred ART, without increased risk for disease progression during the ART interruption period [15]. Nevertheless, we showed that ART interruption is associated with long-term waning of measles protection, hence, suggesting subclinical consequences of ART interruption in these children, which could make them susceptible to measles in the event of outbreaks. Of note, however, is that ART was reinitiated due to CD4+ T-cell depletion, with children being exposed to prolonged HIV viremia during interruption. Seventy percent of children in the main CHER trial had rebounded by 2 months off ART, with median viral load being $\log_5$ HIV RNA copies/mL [40]. The need for further booster doses of measles vaccine in these children is currently being evaluated.

Prior studies reported that if ART initiation precedes immunization, vaccine responses are comparable to those in healthy children [34] and memory B cells are maintained over time [13]. Likewise, our multivariable logistic regression analysis showed that long-term presence of seroprotective titers was associated with being on ART at the time of booster vaccination, as well as at the immunogenicity visit in HIV-infected children, underlining the importance of early and continuous ART.

In contrast to our previous report at 2 years of age (measured in years 2005–2006), where HEU children had lower antibody levels than HIV-unexposed children [25], we did not observe such differences at 4.5 years of age. Possible reasons include that HEU children may have experienced natural boosting of measles antibody titers after exposure to wild-type measles infection [41], especially during the measles outbreak in 2009 in South Africa, which occurred prior to the sampling point for this study [42, 43]. Also, immune system aberrations of HEU children could resolve after the first 2 years of life [22]. Other studies have also reported that HEU children produce robust anamnestic antibody responses to measles vaccination [8, 26–30].

The participants we selected had CD4+ percentage ≥25%, which reduces the generalizability of our findings to HIV-infected children who are already severely immunocompromised by 4–8 weeks of age. Furthermore, we did not assess cellular immunity or avidity of the antibody response. The clinical implication of waning measles antibodies in HIV-infected children in whom ART has been interrupted remains uncertain. Strengths of this study include the early administration of ART in HIV-infected children as per current guidelines, the randomized nature of the ART initiation and interruption, the large sample size, and length of follow-up.

In order to achieve measles elimination by 2020, as targeted by the WHO, it is essential for HIV-infected children to receive timely and complete measles vaccination, in addition to early and continuous ART. This study showed that waning of immunity occurs in HIV-infected children, in particular, if ART has been interrupted, but not in HEU children. In a real-world situation, this may happen with poor adherence or missed visits. To prevent measles outbreaks and achieve sufficient levels of population immunity, HIV-infected children and adolescents may need supplemental immunization, especially if they were not on ART at the time of vaccination or are not currently on ART.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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