Effect of in-utero HIV exposure and antiretroviral treatment strategies on measles susceptibility and immunogenicity of measles vaccine

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Introduction: The high burden of maternal HIV-infection in sub-Saharan Africa may affect measles control. We evaluated the effect of in-utero HIV-exposure and anti-retroviral treatment (ART) strategies on measles antibody kinetics prior and following measles vaccination.

Methods: Infants aged 6–12 weeks were enrolled. This included HIV-uninfected infants born to HIV-uninfected (HUU) and HIV-infected mothers (HEU). Additionally, we enrolled perinatal HIV-infected infants with CD4% equal or greater than 25% randomized to deferred-ART until clinically or immunologically indicated (Group-3) or immediate-ART initiation (Group-4). Group-4 was further randomized to interrupt ART at 1 year (Group-4a) or 2 years of age (Group-4b). Additionally, a convenience sample of HIV-infected infants with CD4⁺ less than 25% initiated on immediate-ART was enrolled (Group-5). Measles immunoglobulin-G antibodies were quantified by an indirect enzyme immunoassay with titers 330 mIU/ml or more considered 'sero-protective'. The referent group was HUU-children.

Results: The proportion with sero-protective titers at 7.3 weeks of age was higher in HUU (65.2%) compared with any HIV-infected group (range: 16.7–41.8%), but dropped to less than 17% in all groups at age 19.6 weeks. Twenty-eight weeks following the first measles vaccine, Group-4a was less likely to have sero-protective titers (79.3%) as compared to HUU (91.1%; P < 0.0001), Group-3 (95.7%; P = 0.003) or Group-4b (92.1%; P = 0.018). Although the proportion with sero-protective levels were similar between groups immediately postbooster dose, this was lower in HEU (79.6%; P = 0.002) and Group-4a (80.3%; P = 0.010) compared with HUU (94.3%) 41-weeks later.

Conclusion: Greater waning of immunity among HIV-infected children in whom ART was interrupted and in HEU following a booster-dose, indicate the possible need for further measles-booster doses after 2 years of age in these children.

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Introduction

Improved immunization of children against measles has reduced measles-associated mortality globally over the past decade [1,2]. Sporadic measles outbreaks persist in many settings, disproportionately involving children too young to be vaccinated [3]. Twenty-four percent of cases in a recent measles outbreak in South Africa were aged less than 9 months [4]. A greater proportion of measlesassociated hospitalization occurs in children aged less than 9 months among HIV-infected (33%) compared with HIV-uninfected African children (23%) [5].

Factors contributing to the sporadic outbreaks of measles include vaccine coverage below the 95% threshold required to interrupt wild-type virus circulation in communities, pockets of susceptible individuals who remain unimmunized or have sub-optimal immune responses to vaccine and reduced transplacental measles antibody transfer to fetuses as maternal immunity is now mainly vaccine induced [2,3,6]. Furthermore, maternal HIV-infection has been associated with lower measles antibody transfer to the fetus and more rapid decay of maternal-derived antibodies in HIV-infected children [7–10].

A recent meta-analysis identified a limited number of studies evaluating the immunogenicity of measles vaccine following primary vaccination in predominantly antiretroviral treatment (ART)-naive HIV-infected children [11]. None of the studies were undertaken in the context of early initiation of ART in HIV-infected children [12]. The meta-analysis reported that 59% [95% confidence intervals (95% CIs), 46-71%] of HIV-infected children were sero-positive after receiving standard-titer measles vaccine at 6, 9 or 12 months of age without any differences by age of vaccination. Fewer HIV-infected children (40%) remained protected compared with HIVexposed, uninfected children 12 months postvaccination [11]. A higher proportion of older HIV-infected children (78-89%) developed sero-protective titers when vaccinated post immune-reconstitution following ART initiation [13,14]. Despite sub-optimal immune responses and higher rates of vaccine failure in HIV-infected children, this was not considered a major hurdle in measles control and elimination because of the high mortality rate in the absence of ART [15]. Improved survival of HIV-infected children on ART may, however, paradoxically impair measles control because of suboptimal immune responses to vaccine [16].

The objectives of our study were: evaluate the effect of in-utero HIV exposure and timing of ART initiation to measles susceptibility prior to vaccination; examine the association of HIV exposure and different ART strategies on the kinetics of measles antibody following the primary and booster doses of measles vaccine.

Methods

Study population

The study was conducted on archived serum samples from children in whom the effects of HIV exposure and timing of ART initiation on immune responses to pneumococcal conjugate vaccine were evaluated [17]. Infants between 6 and 12 weeks of age, were enrolled from April 2005 to June 2006 into five groups: HIVuninfected children born to HIV-uninfected mothers with negative HIV-enzyme linked immunosorbant assay (ELISA) at enrolment (Group-1; HUU); HIV-exposed, uninfected children born to HIV-infected mothers in whom HIV-PCR was negative at enrolment (Group-2; HEU). In parallel, the study co-enrolled HIV-infected children already enrolled into the 'Children with HIV Early Antiretroviral (CHER)' study as described [18]. These included perinatal HIV-infected infants aged less than 12 weeks with CD4% equal to or greater than 25% who were randomized to deferred ART (Group-3) or immediate ART (Group-4) with interruption at approximately 1 year (Group-4a) or 2 years of age (Group-4b). ART initiation and re-initiation were based on WHO immunologic criteria (CD4%<25%; <20% after infancy) or CDC severe B or C clinical disease. Additionally, a convenience sample of HIV-infected infants with CD4⁺ less than 25% initiated on ART at enrolment (Group-5) were recruited. The first-line ART regimen in CHER included zidovudine, lamivudine and lopinavir-ritonavir. Following an interim analysis of the CHER study in which progression to AIDS or death was greater in Group-3 compared with Group-4, the Data, Safety and Monitoring Board recommended that all Group-3 children not yet on ART be immediately started on treatment [18]. In addition to other childhood vaccines administered as described [17], children received the Schwarz-strain measles vaccine (Rouvax; Aventis, France) at age 38-42 weeks and a booster dose at age 64-76 weeks.

Laboratory assays

Clotted blood samples were centrifuged and serum archived at -70° C until processing at the Respiratory and Meningeal Pathogens Research Unit, Johannesburg, South Africa. Samples were analyzed for measles specific IgG antibodies with a commercial indirect ELISA kit (Enzygnost, Dade Behring, Marburg, Germany) and results calibrated against the international reference preparation of measles antibody. Antibody titer levels were calculated using the α -method and presented in milli-International Units per millilitre (mIU/ml) per manufacturer recommendation. Assays with titers less than 150 mIU/ml were considered as negative [equivalent to <0.1 optical density (OD)], 150-329 mIU/ml as equivocal (equivalent to 0.1-0.2 OD) and equal to or greater than 330 mIU/ml as sero-protective (equivalent to >0.2 OD) per manufacturers criteria. For this study, sero-positivity was defined as antibody titers equal to or greater than 150 mIU/ml. Samples for which the OD value was less than 0.1 were assigned a titer of half the detection limit of the assay (i.e. 75 mIU/ml) when calculating geometric mean titers (GMT).

Measles antibody titers were analyzed twice prevaccination at study enrolment (age 6-12 weeks) and approximately 20 weeks of age. Furthermore, measles antibody was measured prior to and 2 weeks after the booster dose, as well as at approximately 2 years of age. No blood was planned *a priori* immediately prior to the first dose of measles-vaccine or anytime soon thereafter.

Statistical analysis

Data was analyzed using GraphPad Prism 5a (GraphPad Software Inc, La Jolla, California, USA). GMTs and 95% CIs were calculated following log_{10} transformation of antibody titers. Comparison of GMTs between groups was done by unpaired *t*-test on log_{10} transformed data. Correlation between measles antibody titer and CD4⁺ percentage was measured using Spearman's correlation coefficients. Proportions of children were compared with chi-square test or Fischer exact test when needed. A *P*-value of 0.05 or less was considered statistically significant. The HUU children were the referent group. Comparisons between the ART strategies in HIV-infected children were also undertaken. Due to the limited number of participants in Group-5, statistical comparisons were not undertaken between this and other Groups.

Ethics

The study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (M080966). The study from which samples were obtained was approved by HREC, the Ethics Committee of Stellenbosch University, Medicine Control Council (South Africa) and the Division of AIDS of the NIH and was registered under Clinical Trials number (NCT00099658).

Results

Samples were available for 528 (91.3%) of 578 children enrolled into the parent study from the initial time-point. The number of samples available at each time-point in the various groups is detailed in Fig. 1. Of the 176 Group-4 children with samples available at the time of the booster dose, 87 had been assigned to discontinue ART at age 12 months and 89 were scheduled to interrupt ART at age 24 months. Forty-eight percent (n=251) of children were male and 90.9% (n=480) black-African descent. The mean age of children at each study time-point, at the time of primary measles vaccination and booster dose was similar between groups (Table 1). The CD4⁺ cell percentage and counts at enrolment and subsequent visits in HIV-infected children are summarized in Table 1 and supplementary-Table S1 (http://links.lww.com/QAD/A321). At a mean age of 19.6 weeks, $CD4^+\%$ were higher in Group-4 (41.6%) compared with Group-3 (29.9%; P = 0.0001) and Group-5 (31.5%; P = 0.003) children (Table 1). Similarly, CD4⁺% remained higher at the time of the first vaccine dose in Group-4 (39.1%) compared with Group-3 (31.0%; P=0.0001) and Group-5 (30.6%; P=0.011). Group-4a had lower CD4⁺% (27.8%) when measured 2 weeks postbooster dose compared with Group-3 (34.5%; P=0.0001) and Group-4b (36.2%; P=0.0001)(Table 1). The median age of ART initiation in Group-3 was 25.0 (18.4-40.0) weeks, and 65.3% (49/75) in this group had been initiated on ART by the time they received the first measles vaccine and 68 (98.6%) of the remaining 69 had been initiated on ART by the time of their booster dose of measles vaccine. Also, 67 (77.0%) of 87 Group-4a children had been re-initiated on ART by the time of their booster vaccine dose.

Prevaccination measles antibody kinetics

The proportion of HUU children who were sero-positive (78.3%) or had sero-protective titers (65.2%) was similar to HEU infants, but higher than in Group-3 (56.3 and 37.9%, respectively) and Group-4 (59.3 and 41.8%) (Fig. 2 and supplementary-Table S2, http://links.lww. com/QAD/A321). Also, GMTs were higher in HUU (963 mIU/ml) compared to Group-3 (657 mIU/ml, P = 0.04; Fig. 2) at enrollment. By 19.6 weeks of age, the proportion of children with sero-positive and seroprotective titers among HUU had declined to 28.9 and 16.7%, respectively; both higher than in Group-3 (5.7 and 0%,) and Group-4 (16.1 and 7.2%) (Fig. 2 and supplementary-Table S2, http://links.lww.com/QAD/ A321). There was no difference in the fold-decrease of antibody titers in HUU (0.49) compared with HEU (0.39, P=0.21), Group-3 (0.31, P=0.97) and Group-4 (0.42, P=0.96) between enrollment and 19.6 weeks of age (supplementary-Table S2, http://links.lww.com/ QAD/A321).

Antibody kinetics postprimary and booster doses of measles vaccine

The first measles vaccine was administered at 39.7 (SD \pm 2.3) weeks of age. Twenty-eight weeks thereafter (study visit 3), the proportion of HUU children with sero-positive (93.8%) or sero-protective titers (91.1%) was similar to other groups, except for a lower proportion of Group-4a (79.3%; *P* < 0.0001) having sero-protective titers (Fig. 3 and supplementary-Table S3, http://links.lww.com/QAD/A321). This occurred despite 77.0% (67 of 87) Group-4a children already having been re-initiated on ART at this stage. Group-4a were also less likely to have sero-protective titers compared to Group-3 (95.7%; *P*=0.003) and Group-4b (92.1%; *P*=0.018;

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Fig. 1. Subject follow-up during the duration of the study. ^aHUU: HIV-uninfected children born to HIV-uninfected mothers (Group-1); ^bHEU: HIV-uninfected children born to HIV-infected mothers (Group-2); ^cGroup-3: HIV-infected children on deferred ART; ^dGroup-4: HIV-infected children on immediate ART; ^eGroup-5: HIV-infected children with CD4% less than 25% on immediate ART; ^fGroup-4a: HIV-infected children who interrupted ART at 12 months of age; ^gGroup-4b: HIV-infected children who continued ART till 24 months of age. Insufficient sample: sample unavailable for further testing; LFTU: loss to follow-up due to relocation or the child stopped the study without reason; Withdrawal: parent or guardian withdrew informed consent; Missed visit: children missed a schedule visit; number of participants who left the study (LTFU, withdrawals, deceased) are represented as cumulative at each visit. ^hNumber in parenthesis are percentages of total enrolled; Group-4a and Group-4b combined: at visit 3 96.7%, at visit 4 94.5% and at visit 5 69.8%.

Fig. 3); and also had lower GMTs compared with each of the other Groups at this time-point (Fig. 3).

The booster dose was given at 67.8 (SD \pm 4.4) weeks of age, after which the proportion of children with sero-protective titers was equal to or greater than 90.2% and did not differ between groups when evaluated 1.9 weeks (SD \pm 0.1) later (Fig. 3 and supplementary-Table S3, http://links.lww.com/QAD/A321). The GMTs postbooster were higher in HUU (3124 mIU/ml) compared with HEU (2532 mIU/ml, P=0.015) and Group-4a (1435 mIU/ml, $P \leq 0.0001$) (Fig. 3). GMTs in Group-4a also remained lower compared with Group-3 (3254 mIU/ml, P < 0.0001) and Group-4b (2740 mIU/ml, P=0.002) postbooster dose (Fig. 3). The proportion of Group-5 children with sero-protective titers was 100% postprimary and postbooster vaccine.

Persistence of antibody was evaluated 41.4 (S.D. \pm 0.3) weeks following the booster dose, at approximately 111

weeks of age, by when HUU were more likely to have sero-protective titers (94.3%) compared with HEU (79.6%; P=0.002) and Group-4a (80.3%; P=0.010) (Fig. 3 and supplementary-Table S3, http://links.lww. com/QAD/A321). Although 75.4% (46/61) of Group-4a children had been re-initiated on ART by this time-point, they remained less likely to have sero-protective titers compared to Group-3 (96.0%; P=0.013) and similarly to Group-4b (86.4%; P=0.360). At the same time-point, GMTs were higher in HUU (2248 mIU/ml) compared to HEU (1773 mIU/ml, P=0.004) and Group-4a (1156 mIU/ml, P<0.0001) (Fig. 3). Group-4a also had lower GMTs compared with Group-3 (2577 mIU/ml) P<0.0001) and Group-4b (1924 mIU/ml, P=0.009).

Discussion

To our knowledge, this is the first study which systematically evaluated the kinetics of measles antibody

Characteristics	Group-1 (HUU) ^a	Group-2 (HEU) ^b	Group-3 ^c	Group-4 ^d		Group-5 ^e	Total
Enrolment	N = 115	N=116	N = 103	N=182		N = 12	N=528
Mean age, weeks \pm SD	6.9 ± 1.0	7.3 ± 1.0	7.3 ± 1.1	7.4 ± 1.3		8.4 ± 1.5	7.3 ± 1.2
Mean $CD4^+$ cell % ± SD	NA	NA	36.5 ± 1.1	35.4 ± 0.6		22.0 ± 1.9	NA
Premeasles vaccination	N = 114	N = 112	N = 70	N = 180		N = 7	N = 483
Mean age, weeks \pm SD	19.3 ± 1.7	19.5 ± 1.1	19.7 ± 1.7	19.7 ± 1.6		20.7 ± 1.5	19.6 ± 1.6
Mean $CD4^+$ cell $\% \pm SD$	NA	NA	$29.9 \pm 1.0^{\rm f}$	41.6 ± 0.7^{f}		31.5 ± 2.1	NA
1st measles vaccine	N = 115	N = 116	N = 75	N = 182		N = 10	497
Mean age, weeks \pm SD	38.9 ± 1.0	39.4 ± 1.6	40.8 ± 3.9	39.8 ± 2.0 $39.1 \pm 0.6^{\text{f}}$		41.5 ± 2.9	$39.7\pm\!2.3$
Mean $CD4^+$ cell $\% \pm SD$	NA	NA	31.0 ± 0.9^{f}			30.6 ± 2.7	NA
				Group-4a ^g	Group-4b ^h		
Measles booster	N = 112	N = 116	N = 69	N = 87	N = 89	N = 8	N = 481
Mean age, weeks \pm SD	67.2 ± 5.0	67.1 ± 2.2	69.3 ± 7.7	68.0 ± 1.9	67.8 ± 2.1	67.9 ± 1.5	67.8 ± 4.4
2 weeks postbooster	N = 115	N = 114	N = 68	N = 82	N = 90	N = 8	N = 477
Mean age, weeks \pm SD	69.3 ± 5.4	$69.4\pm\!2.8$	72.1 ± 6.8	69.7 ± 2.2	69.3 ± 2.2	69.4 ± 1.5	70.2 ± 5.4
Mean $CD4^+$ cell $\% \pm SD$	NA	NA	34.5 ± 0.9^{i}	27.8 ± 0.9^{i}	36.2 ± 0.9^{i}	29.4 ± 3.4	NA
6 weeks postbooster	N = 115	N = 114	N = 68	N = 82	N = 90	N = 8	N = 477
Mean age, weeks \pm SD	69.3 ± 5.4	69.4 ± 2.8	72.1 ± 6.8	69.7 ± 2.2	69.3 ± 2.2	69.4 ± 1.5	70.2 ± 5.4

Table 1.	Age and CD4 ⁺	lymphocyte	percentage at	different study	time-points.
	a	/			

NA, not available.

^aHUU, HIV-uninfected children born to HIV-uninfected mothers (Group-1).

^bHEU, HIV-uninfected children born to HIV-infected mothers (Group-2).

^cGroup-3, HIV-infected children on deferred ART.

^dGroup-4, HIV-infected children on immediate ART.

^eGroup-5, HIV-infected children with CD4% less than 25% on immediate ART.

 $^{f}P \le 0.001$ comparing Group-3 vs. Group-4.

^gGroup-4a, HIV-infected children who interrupted ART at 12 months of age.

^hGroup-4b, HIV-infected children who continued ART till 24 months of age.

 $P \le 0.001$ comparing Group-3 vs. Group-4a and Group-4a vs. Group-4b. N = total number of children with available sample.

pre- and post-vaccination in HIV-infected children managed according to the current WHO recommendations of immediate initiation of ART upon diagnosis of HIV in infants; [12] and also the first study to examine the effect which interruption of ART in healthy 1-year old immunologically stable HIV-infected children had on measles antibody kinetics. Significant findings of our study included the high susceptibility to measles infection as early as 7 weeks of age in the majority of HIV-infected children and in more than 83% of all groups by 20 weeks of age. Also, interruption of ART in HIV-infected children (Group-4a) was associated with them being less likely to have sero-protective levels 28-weeks following the primary dose of measles-vaccine and less likely to maintain sero-protective titers 9.5 months after the booster dose. Furthermore, there was also waning of immunity in HEU children 9.5 months postbooster indicated by a lower proportion with sero-protective titers and lower GMTs compared with HUU. This despite, the proportion of HEU with sero-protective titers being similar compared with HUU children following the initial and immediately following the booster dose.

This high susceptibility to measles in children under 6 months is corroborated by other African studies in HIV-infected (85–91%) and HEU children [19,20], and more recently among healthy infants in developed countries [3]. In developed countries, the increased susceptibility to measles infection among young infants has been attributed to decrease in passive immunity

acquired from transplacental maternal measles antibody transfer, because of lower measles antibody levels in pregnant women who acquired immunity from vaccination rather than by natural infection [21]. Additional factors, which may contribute to the increased immunological susceptibility to measles infection in infants born to HIV-infected mothers compared with HUU infants, include lower measles antibody titers and impaired transplacental transfer of antibody in HIV-infected mothers [9]. Also, there may be greater decay of antibody in HIVinfected children [22]. The observation that GMTs and proportion of children with sero-protective titers were similar between HUU and HEU children suggests that factors other than solely maternal HIV positivity contributed to increased susceptibility to measles at an earlier age in HIV-infected children. Possible reasons include that mothers' of peripartum HIV-infected children had higher HIV viral load, which has been associated with increased perinatal HIV transmission and inversely associated with efficiency of trans-placental transfer of measles antibody [7,23,24].

The WHO has recommended that in settings of high HIV prevalence, infants should receive two doses of measles vaccine at 6 and 9 months of age [2]. This recommendation has, however, not been widely implemented; for example in South Africa the initial dose is still scheduled for 9 months of age. Reasons for this include the inherent low immunogenicity of measles vaccine in younger children, coupled with interference in the immune response by prevailing maternal-derived measles



Fig. 2. Geometric mean titers and proportion of infants with sero-positive and sero-protective levels of measles antibody premeasles vaccination. Group-1(HUU): HIV-uninfected children born to HIV-uninfected mothers; Group-2 (HEU): HIV-uninfected children born to HIV-infected mothers; Group-3: HIV-infected children on deferred ART; Group-4: HIV-infected children on immediate ART; Group-5: HIV-infected children with CD4% less than 25% on immediate ART. (a) Measles geometric mean titers at visit 1 and visit 2. Vertical bars represent 95% CI. ^a*P*-value = 0.04 in relation to Group-1. (b) Proportion of infants sero-positive (\geq 150 mIU/mI) and sero-protected (\geq 330 mIU/mI) at visit 1 and visit 2. ^a*P*-value = 0.001 in relation to Group-1; ^b*P*-value < 0.001 in relation to Group 1; ^c*P*-value = 0.01 in relation to Group-1.

antibody [25–27]. Based on our study, the low prevalence of maternal-derived antibody in young infants (<30% at 20 weeks of age) supports immunization at 6 months of age. A recent report from Guinea–Bissau indicated that vaccination as early as 4.5 months of age using the Edmonston–Zagreb measles vaccine strain induced seroprotective antibody levels in 77% of infants, as well as being associated with 94% efficacy against measles infection [28].

A limitation of our study includes that immune response following the first dose of measles vaccine was only evaluated 8 months after vaccination, as earlier evaluation had not been planned *a priori* in the parent study. Consequently, although we were unable to undertake a direct comparison of immune responses in the overall Group-4 compared with other Groups, Group-4b may be representative of the initial Group-4 cohort at least until 2 years of age. Persistence of antibody levels up until prior to the booster dose was similar in HUU compared with Group-4b, as well as the surviving children in Group-3. This indicated that the timing of ART did not affect immune responses to measles vaccine in those HIVinfected children with CD4⁺ more than 25% at enrolment. We have, however, previously reported higher early-childhood mortality rate in Group-3 compared with Group-4 children [18]. Additionally, 100% of Group-5 children also had persistence of sero-protective titers 8 months postprimary dose. The good immune responses in HIV-infected children on ART corroborate reports that initiation of ART in the first year of life allows the normal development of T-cell and B-cell immunity [29-31].

Although the proportion of Group-4a with seroprotective titers 2-weeks following the booster dose of vaccine was similar (>90%) to the other Groups, their GMTs were lower compared with other Groups immediately postbooster dose. Furthermore, greater waning of immunity was observed in Group-4a following the initial and after the booster-dose, despite them being carefully monitored for clinical and immunological disease progression following ART interruption at 12-months of age, resulting in ART being re-initiated in 77% of them at the time of the booster dose. $CD4^+$ cell counts and percentage were however lower in Group-4a compared with Group-3 and Group-4b immediately following the booster dose. This indicated that interruption of ART in Group-4a resulted in waning of immunity, including possibly decline in anamnestic responses to measles. This may be explained by the deterioration of antigen specific pools of memory B cells in the absence of ART [31]. The proportion of Group-4a who had sero-protective titers at approximately 2-years of age was, however, higher compared with ART-naive HIV-infected children who had been vaccinated at 6 and 9 months of age and assessed at 20 months of age (41%) as reported by Fowlkes et al. [32].

In exploring the effect of HIV exposure on persistence of measles antibody following vaccination, we observed that GMTs were higher in HEU compared with HUU children prior to the booster dose. Lower prevaccination antibody levels in HEU children have been previously reported to be associated with more robust immune responses to some vaccines during early childhood [33]. This was, however, unlikely to be the reason for the higher GMTs in HEU in our study as prevaccination measles antibody levels were similar to that of HUU children. The clinical relevance of the higher GMTs in HEU is unclear as the proportion of children with seroprotective titers was similar between the two groups. The higher GMTs in HEU children prior to the booster dose is also difficult to explain in the context of lower GMTs



Fig. 3. Geometric mean titers and proportion of infants with sero-positive and sero-protective levels of measles antibody following primary and booster vaccine. Group-1(HUU): HIV-uninfected children born to HIV-uninfected mothers; Group-2 (HEU): HIV-uninfected children born to HIV-infected mothers; Group-3: HIV-infected children on deferred ART; Group-4: HIV-infected children on immediate ART; Group-5: HIV-infected children with CD4% less than 25% on immediate ART. Group-4a: HIV-infected children who interrupted ART at 12 months of age; Group-4b: HIV-infected children who continued ART till 24 months of age. (a) Measles geometric mean titers at visit 3 (preboster), visit 4 (1.9 weeks postbooster) and visit 5 (41.4 weeks postbooster). Vertical bars represent 95% confidence interval. ^a*P*-value <0.02 in relation to Group-1; ^b*P*-value <0.001 in relation to Group-4a. (b) Proportion of infants sero-positive (\geq 150 mIU/mI) and sero-protected (\geq 330 mIU/mI) at visit 3, visit 4 and visit 5. ^a*P*-value <0.04 in relation to Group-1; ^b*P*-value <0.02 in relation to Group-3, ^c*P*-value = 0.02 in relation to Group-4a.

being observed 2-weeks thereafter in this Group compared with prebooster levels, as well as relative to HUU children postbooster. Lower GMTs persisted in HEU compared with HUU until 9.5 months postbooster, at which time HEU were also less likely to be sero-positive or have sero-protective titers. The underlying immune aberration which may cause waning of immunity in HEU, as well as the need for further booster doses of vaccine in these children remain to be explored.

Limitations of our study included only having a convenience sample of HIV-infected children with CD4⁺ less than 25% at screening (i.e. Group-5). Nevertheless, the observations in this group were similar to those of HIV-infected children on ART (i.e. Group-4b), suggesting that CD4⁺ percentage categorization at enrolment did not have an effect of immune responses to measles vaccine in children who had been initiated on ART upon confirmation of being HIV-infected. Furthermore, our study involved measuring measles antibody by ELISA as a surrogate of protection, which have been shown to miss low antibody level responses [34], rather than the plaque reduction neutralization assay which correlates more strongly with protection [35]. We may therefore have over-estimated the protection against measles infection, particularly among HIV-infected children in whom poorer IgG avidity may affect neutralizing activity which has, however, only been observed in the absence of ART [36].

In conclusion, our study indicates that persistence of maternal measles antibody does not any longer appear to being an impediment to measles vaccination by 6 months of age, possibly with the Edmonston–Zagreb vaccine strain, irrespective of the child's HIV infection status [11]. Reasonably good responses have been observed in ART-naive HIV-infected children when immunized with an Edmonston–Zagreb vaccine strain as early as 6 months, followed by a booster dose at 12 months of age [37]. Sustainability of protection and need for further doses of measles vaccine in HIV-infected children in whom ART has been interrupted and in HEU remains to be explored, as does the issue of sustainability of protection in HIV-infected children who are maintained on ART.

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Conflicts of interest

There are no conflicts of interest.

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