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Sustained Responses to Measles Revaccination at 24 Months in HIV-Infected Children on Antiretroviral Therapy in Kenya

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Abstract

Background—There are limited data on whether HIV-infected children in resource-limited countries who are receiving antiretroviral therapy (ART) are able to produce sustained, protective levels of measles antibody after multiple measles vaccinations.

Methods—We administered an additional measles vaccine to HIV-infected children 15 months to 12 years of age receiving ART in Nairobi, Kenya. Measles antibody concentrations were determined by enzyme-linked immunosorbent assay (ELISA) at enrollment, one month, 12 months, and 24 months post revaccination.

Results—At enrollment, 125 (54%) of 232 study participants had protective concentrations of measles antibody. Measles seropositivity increased to 98% of all children at one month post revaccination, but decreased to 71% at 12 months, and 60% at 24 months post revaccination. Measles seroconversion and sustained measles seropositivity among those who were measles seronegative at enrollment was 25% at 24 months post revaccination. In this group, 39% of children with <50 copies/mL plasma HIV RNA measles seroconverted compared with 4% of children with plasma HIV RNA ≥1,000 copies/mL ($p=0.018$).

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Conclusions—Measles revaccination can result in a sustained antibody response in a subset of HIV-infected children receiving ART, especially among those with HIV suppression.

Keywords

measles vaccination HIV children

INTRODUCTION

Despite advances in reducing overall measles incidence in Africa¹, several large and deadly measles outbreaks have occurred in countries with high adult and child HIV prevalence². HIV infection reduces both initial and sustained immune responses to measles vaccination. A single measles vaccine at 9 months of age confers immediate protection to 25%–88% HIV-infected infants^{3–5}, substantially lower than 85–95% response rates among HIV uninfected infants^{6–8}. Further, even in HIV-infected infants with an adequate initial response, fewer than 50% maintain protective antibody levels after one year^{4,5}. Vaccination after initiation of antiretroviral therapy (ART) may improve the response; however, many HIV-infected infants are not diagnosed and treated before receiving routine measles vaccination⁹.

In areas with high incidence of both HIV and measles, the World Health Organization (WHO) suggests the first measles vaccine may be offered as early as age 6 months, followed by two additional doses according to the national immunization schedule^{10,11}. However, the scope and frequency of early routine immunization and SIA vary by country, and many countries have yet to implement these recommendations¹¹. In October 2015, the WHO Strategic Advisory Group of Experts (SAGE) recommended an additional dose of measles-containing vaccine for HIV-infected children receiving highly active antiretroviral therapy following immune reconstitution, but stated that further research is needed to monitor the long-term immune responses to measles vaccination in HIV-infected children revaccinated after starting ART¹².

We administered an additional measles vaccine to HIV-infected children on ART in Nairobi, Kenya, and determined the prevalence of measles seropositivity after one, 12, and 24 months. Additionally, we explored factors associated with measles seroconversion at 24 months post revaccination among the HIV-infected children who were measles seronegative at enrollment.

MATERIALS AND METHODS

Study participants and procedures

HIV-infected children and their caregivers were recruited from the HIV Comprehensive Care Centre at Kenyatta National Hospital in Nairobi, Kenya, during routine HIV care visits between May 2011 and January 2013, as previously described¹³. Caregivers willing to be screened were asked to read and sign an informed consent document, approved by Kenyatta National Hospital and the University of Washington. Children above the age of seven years

were asked to assent to participation. Those eligible who chose not to enroll were given access to measles vaccination at no cost.

Eligibility criteria included age between 15 months and 12 years, HIV infection confirmed by HIV-1/2 ELISA and/or PCR, on ART at the time of enrollment, and CD4% ≥ 15 . Child exclusion criteria included a history of adverse reaction to measles vaccination, allergy to gelatin or neomycin, hospitalization within the preceding two weeks, blood or plasma transfusion or receipt of immune globulin within last six months.

At enrollment, demographic and medical history was collected from caregivers and immunization and treatment information from clinical charts. Each child was examined and received a measles vaccination (Serum Institute of India or Vaksin Campak Kering Indonesia). Blood draws were obtained from children at enrollment, one, six, 12, and 24 months after revaccination.

Laboratory assays

Serum measles IgG was determined at enrollment, one, 12, and 24 months post revaccination. CD4% was determined at enrollment, six, 12, and 24 months post revaccination in accordance to standard monitoring practice. Plasma HIV RNA was determined at enrollment, 12, and 24 months post revaccination. Serum measles IgG antibodies were measured using an ELISA (Enzygnost, Germany). Optical density (OD) values were determined and values >0.1 OD were converted into measles-specific IgG mIU/mL using manufacturer's calculations based on the First International World Health Organization Reference Preparation Standards.

CD4% was determined by the University of Nairobi Paediatrics Laboratory, Kenya (FACSCalibur, BD Biosciences, USA). To determine plasma HIV RNA, samples were stored at -80°C on site, and frozen samples were shipped to the University of Washington (UW), USA. Plasma HIV RNA levels were measured by the Gen-Probe HIV-1 RNA assay (Gen-Probe, San Diego, CA), which has been validated on the HIV subtypes prevalent in Kenya¹⁴. An exploratory analysis of cytomegalovirus (CMV) DNA quantification in plasma was performed, based on previous studies that suggest CMV infection was associated with impaired responses to vaccination¹⁵. CMV was determined at baseline in a subset of participants at UW by real-time PCR¹⁶.

Vitamin A levels were determined by measuring retinol binding protein (RBP), C-reactive protein (CRP), and α -1-acid-glycoprotein (AGP) using a sandwich enzyme-linked immunosorbent assay (ELISA) technique¹⁷. Final determination of RBP concentration was adjusted in cases where CRP and AGP, markers for inflammation, were elevated^{18,19}.

Statistical analyses

We defined response to measles revaccination in two ways: measles seropositivity (a measles IgG titer ≥ 200 mIU/mL at any time point), and measles seroconversion (an increase in measles IgG antibody titer from seronegative [measles IgG titer <200 mIU/mL] to seropositive levels at one, 12, or 24 months post revaccination)²⁰. We categorized plasma HIV RNA as <50 copies/mL, 50–999 copies/mL, and $\geq 1,000$ copies/mL based on the WHO

definition of virologic failure in children²¹. Underweight (defined as a weight-for-age z-score <-2), wasted (defined as a weight-for-length/height z-score <-2), and stunted (defined as a length/height-for-age z-score <-2) were calculated using child growth standards developed by the WHO (WHO Anthro macroversion 3.2.2, January 2011)²². Severe vitamin A deficiency was defined as an adjusted RBP concentration of <0.7 $\mu\text{mol/L}$, and moderate deficiency as an adjusted RBP concentration of $0.7 - 1.05$ $\mu\text{mol/L}$ ¹⁹.

To determine whether early vaccine response predicted durability, we assessed whether those who were measles seropositive at 24 months post revaccination had similar or higher antibody titers at 1 and 12 months post revaccination. Seronegative antibody levels were assigned a random number between 0 and 2.30 on the $\log_{10}$ scale for these comparisons. To determine whether revaccination resulted in an increased proportion of those measles seropositive at 24 months post revaccination, we estimated the risk of measles seropositivity at 24 months by log-binomial regression with robust error variance. The potential association of baseline characteristics and measles seropositivity at 24 months was evaluated in univariate log-binomial regression models with robust error variance. Characteristics that were statistically significantly associated with measles seropositivity at 24 months post revaccination were included in a multivariate model. Baseline characteristics assessed included age, sex, measles serostatus at enrollment, CD4%, plasma HIV RNA, time on ART, WHO Stage, vitamin A deficiency, length/height-for-age z-score, and stunting. Biological plausibility and graphical techniques were used to find biologically relevant cutoffs for continuous correlates. Among 156 participants who were assessed for baseline CMV viremia, Pearson chi-square was used to test differences in active CMV infection by measles serostatus at 24 months.

Maintenance of measles seropositivity after revaccination may involve a different immunological mechanism than measles seroconversion²³, thus a separate analysis was performed to explore factors associated with seroconversion. We assessed the risk of measles seroconversion at 24 months post revaccination by log-binomial regression with robust error variance. The same baseline characteristics as mentioned above were evaluated for an association with measles seroconversion at 24 months post revaccination in both univariate and multivariate models. Analysis was performed using Stata (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP).

RESULTS

Cohort description

Of 272 children screened, 232 were enrolled and revaccinated. Cohort and caregiver characteristics, as well as measles serostatus before revaccination were previously described¹³. Of the enrolled children, 220 (95%) attended their one month post revaccination visit, 224 (97%) attended their 12 month visit, and 220 (95%) attended their 24 months visit.

Of 232 enrolled children, 228 (98%) had received at least one measles vaccine before one year of age. Boys comprised 53% of the cohort; median age was 7.5 years (IQR: 5.5–9.5 years); and median CD4% was 32 [interquartile range (IQR) 27–38]. Of 216 (93%) children with recorded date of ART initiation, median time on ART was 3.4 years (IQR: 1.8–4.9). At

enrollment, 148 (70%) children were recorded as having advanced stages of HIV (WHO Stage III or IV). Though all children were on ART, only 40% had undetectable levels of HIV RNA <50 copies/mL, and 23% had plasma HIV RNA 1000 copies/mL. Fifty-nine (26%) of 229 children had low serum vitamin A levels: 52 (23%) with moderate deficiency, and 7 (3%) with severe deficiency. Correction of RBP by CRP and AGP did not affect vitamin A deficiency classification. As measured by a length/height-for-age z-score <-2, 54 (23%) children were stunted (Table 1).

Measles serostatus at one, 12, and 24 months post revaccination

Prior to revaccination, 125 (54%) of 232 participants were measles seropositive. This is higher than what was previously reported (48%) due to an updated classification of seropositivity and increased ELISA assay sensitivity¹³. CD4% was a correlate of seropositivity at enrollment: 49% of participants with a CD4% ≥25 had seropositive measles antibody titers compared to 30% of participants with a CD4% <25 (risk ratio [RR]=2.11, 95% CI 1.04, 2.70, p=0.035)¹³. Fifty nine percent of children with a plasma HIV RNA <50 copies/mL were measles seropositive at enrollment, compared to 49% with plasma HIV RNA 50–99 copies/mL (p=0.36) and 44% with plasma HIV RNA ≥1000 copies/mL (p=0.09).

Among the entire cohort at one month post revaccination, 216 (98%) of 220 children were measles seropositive. This proportion decreased to 158 (71%) of 224 at 12 months post revaccination, and 132 (60%) of 220 at 24 months post revaccination (Figure 1). Two participants reported additional measles vaccinations through supplementary immunization activities and both were measles seropositive at all time points.

Among the 125 children who were measles seropositive at enrollment, all remained seropositive at one month post revaccination. By 12 months post revaccination, 117 (98%) of 120 maintained their measles seropositivity, decreasing slightly to 107 (91%) of 118 by 24 months (Figure 1). Eleven participants who were measles seropositive at enrollment reverted by 24 months; nine had measles-specific IgG antibody titers close to the seropositive threshold at all timepoints, and two participants had antibody titers well above the threshold at enrollment, with CD4% at or above 30 and <50 copies/mL plasma HIV RNA at all timepoints.

Among the 107 children who were measles seronegative at enrollment, 98 (94%) of 102 seroconverted at one month post revaccination. Among four children who failed to seroconvert, three had plasma HIV RNA levels between 4,417 and 693,650 copies/mL. Forty-one (39%) of 104 sustained measles seropositivity at 12 months, and 26 (25%) of 102 sustained seropositivity at 24 months post revaccination (Figure 1). In participants who were measles seropositive at 24 months post revaccination, early responses to revaccination were better, as measured by mean measles log₁₀ IgG titer. At one month post revaccination, mean log₁₀ IgG was 3.24 in those measles seropositive at 24 months compared to a mean log₁₀ IgG of 2.85 among those who were seronegative at 24 months (p=0.001). At 12 months, those who were measles seropositive at 24 months also had higher levels than those who were measles seronegative at 24 months (mean log₁₀ IgG=2.53 vs. log₁₀ IgG=1.45, respectively, p<0.001) (Figure 2).

Baseline factors associated with measles seropositivity at 24 months post revaccination

In univariate models, children who were measles seropositive at enrollment were 3.6 times as likely to remain measles seropositive at 24 months post revaccination compared to those who were measles seronegative at time of revaccination (RR=3.56, 95% CI 2.54 – 4.99, $p<0.001$). Children with a CD4% ≥ 30 at enrollment were more likely to remain seropositive compared to those with a CD4% <30 (RR=1.43, 95% CI 1.10 – 1.85, $p=0.007$). Children with a plasma HIV RNA ≥ 1000 copies/mL at time of revaccination were less likely to be measles seropositive compared to those with <50 copies/mL plasma HIV (RR=0.56, 95% CI 0.39 – 0.82, $p=0.002$). There were no statistically significant associations between baseline age, sex, time on ART, WHO stage, nutritional status, or vitamin A status and measles seropositivity at 24 months post revaccination. In multivariate analyses, both measles serostatus at baseline (adjusted Risk Ratio [aRR]=3.43, 95% CI 2.45 – 4.80, $p<0.001$) and plasma HIV RNA (aRR=0.67, 95% CI 0.51 – 0.87, $p=0.003$) remained significantly associated with measles seropositivity at 24 months. A second multivariate model that included CD4% and measles serostatus at baseline was run due to collinearity between plasma HIV RNA and CD4%. CD4% was not significantly associated with measles seropositivity at 24 months after adjusting for measles serostatus at baseline ($p=0.77$) (Table 2).

Twenty-eight (18%) of 156 children had detectable CMV viremia at baseline. Of the 74 who were measles seropositive at 24 months, 11 (15%) had CMV viremia, compared to 17 (20%) of 82 who were measles seronegative at 24 months ($p=0.34$).

Factors predictive of measles seroconversion at 24 months post revaccination

We investigated factors that were associated with measles seroconversion at 24 months post revaccination among those who were measles seronegative at baseline. In univariate models, children with plasma HIV RNA ≥ 1000 copies/mL were 90% less likely to seroconvert and maintain measles antibody seropositivity compared to children who had plasma HIV RNA <50 copies/mL (RR=0.09, 95% CI 0.01 – 0.65, $p=0.017$). Thirty-nine percent of children with <50 copies/mL plasma HIV RNA at enrollment seroconverted at 24 months post revaccination, compared to 17% of children with plasma HIV RNA 50–999 copies/mL, and 4% of children with a plasma HIV RNA ≥ 1000 copies/mL (Table 3).

In univariate models, there was a trend toward larger length/height-for-age z-score at enrollment being associated with measles seroconversion at 24 months post revaccination (RR=1.29, 95% CI 0.99 – 1.68, $p=0.063$). Neither CD4%, nor moderate vitamin A deficiency was significantly associated with measles seroconversion at 24 months, but of the 4 participants who had vitamin A deficiency, none seroconverted at 24 months. Stunting, WHO stage, time on ART, age, and sex were not statistically significantly associated with measles seroconversion (Table 3).

A multivariate model that included CD4% and length/height-for-age z-score resulted in risk estimates similar to univariate analyses; CD4% stayed moderately significant ($p=0.060$), while length/height-for-age z-score was statistically significant ($p=0.036$). A second multivariate model that included plasma HIV RNA and length/height-for-age z-score was

run due to collinearity between plasma HIV RNA and CD4%. Plasma HIV RNA <50 copies/mL remained significantly associated with measles seroconversion at 24 months when compared to plasma HIV RNA ≥1000 copies/mL (adjusted relative risk (aRR)=0.09, 95% CI 0.01 – 0.67, p=0.018), and length/height-for-age z-score was not significantly associated with measles seroconversion at 24 months (p=0.11)(Table 4).

DISCUSSION

In this prospective study of the immunogenicity of measles revaccination in HIV-infected Kenyan children on ART, we found that 54% of children were measles antibody seropositive before revaccination, 71% of children were measles seropositive at 12 months, and 60% of children were measles seropositive at 24 months after revaccination. This is the largest study to describe the long-term immunogenicity of measles revaccination in HIV-infected children on ART in sub-Saharan Africa.

Children in this Kenyan cohort did not respond to measles revaccination as well as other reported cohorts. A study in the United States (US) found that approximately half of HIV-infected children lacked protective levels of measles antibody despite more than 80% coverage with two doses of the measles, mumps, and rubella (MMR) vaccine²⁴. Two months after revaccination, seropositivity increased to 89%, and remained at 80% one and a half years post revaccination²⁴. In Thailand, Arpibul et al. found that 42% of HIV-infected children on ART had protective levels of measles antibody, which increased to 90% one month after revaccination and fell to 85% by 3 years after revaccination^{25–27}. One reason for the differences may be HIV suppression, as 97% of children in the Thailand cohort were HIV suppressed²⁵. In the US cohort, approximately 60% of children had low or <50 copies/mL levels of HIV suppression, which is similar to this Kenyan cohort.

Measles seropositivity at time of revaccination was the strongest predictor of measles seropositivity at 24 months post revaccination, though plasma HIV RNA was also associated with maintaining measles seropositivity or seroconverting. Among those who were measles seronegative at enrollment, plasma HIV RNA was a significant predictor of measles seroconversion at 24 months post revaccination, even in multivariate models. HIV infection affects the quantity and quality of antibody response to measles vaccination^{28–30}, and initiation of ART after measles vaccination is not sufficient to restore measles antibody response³. As in our study, other studies of measles revaccination in HIV-infected children on ART found that the response was related more to suppressed HIV replication than to CD4%^{24,31}. This suggests that the ability to sustain an immune response to measles vaccination may be hindered by high levels of HIV replication, which is associated with turnover and depletion of B and T cells needed for memory²³.

Results from this study may inform policy aimed at reducing measles transmission. Measles is targeted for elimination in five WHO Regions by 2020³². A challenge to this goal is the infectious nature of measles, as it requires 95% of population immunity to interrupt transmission³³. The current WHO SAGE guidelines recommend an additional dose of measles-containing vaccine for HIV-infected children receiving ART following immune reconstitution. This study suggests plasma HIV RNA measurement may be more indicative

of immune reconstitution for the purpose of measles revaccination than CD4% measurement. In settings where measurement of plasma HIV RNA is not available, measurement of immune reconstitution when CD4 reaches 20–25%, or 6–12 months after initiation of ART if CD4 monitoring is not available, as recommended by the WHO, is appropriate¹². Special attention to immunization in children with HIV may be necessary to reach elimination goals. The current measles immunization policy for HIV-infected infants in Kenya is to provide two routine vaccines at 6 and 9 months of age. This policy may be increasingly implemented as early infant HIV diagnosis is scaled up, however it does not impact the more than 100,000 estimated children already living with HIV in Kenya³⁴. Between 2005 and 2015, five SIA campaigns were conducted in response to measles outbreaks³⁵, typically focusing on children under five. Our study demonstrates that a susceptible population of older HIV infected children may not be targeted by SIA campaigns. As such, measles vaccination campaigns could be facilitated through HIV care clinics, especially during measles outbreaks. HIV-infected children on ART attend clinic every few months to receive a prescription refill and for disease monitoring, so a clinic-based delivery system could directly access this susceptible group in a manner that minimizes additional human and physical resources.

While this study had excellent follow-up and retention, there were several limitations. We used ELISA to determine protection against clinical measles and the gold standard for determining protection against measles is a plaque reduction neutralization (PRN) technique. ELISA results are closely associated with PRN, though they lack sensitivity to detect low levels of measles antibody³⁶. However, the smallest antibody concentration detectable using our ELISA is approximately 200mIU/mL, which is a higher titer than what is considered minimally protective against clinical measles²⁰. Since we are not measuring cellular response to measles infection, we cannot assume lack of clinical protection in those with antibody levels below this threshold, though a study done in a subset of this cohort suggests that durable antibody response may correspond to lower T cell activation and anergy³⁷. Another limitation is the use of retinol-binding protein as a surrogate for vitamin A, however, retinol binding protein is a sensitive and specific surrogate measure of plasma retinol^{17,38}, even in HIV-infected individuals³⁹, and is often used as a reliable surrogate.

Because we revaccinated all children, we cannot compare how many children who were measles seropositive at time of revaccination would have remained measles seropositive in the absence of revaccination. Annual measles cases in Kenya during the study ranged from 190 in 2013 to 2,395 in 2011⁴⁰. No children displayed clinical characteristics of measles infection during study follow-up, and the study was designed to mimic the potential benefit of measles revaccination in a population of HIV-infected children who do not undergo routine measles antibody titers.

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Figure 1.

Measles serostatus of HIV-infected children on antiretroviral therapy at enrollment, one month, and 24 months post measles revaccination

¹ Eight participants who have measles serostatus data at 24 months are not included in this figure due to missing data from 1 month. These participants missed the month 1 visit but returned at the 24 month visit. At both enrollment and 24 months, three were measles seronegative and five were measles seropositive.

Figure 2.
Mean measles $\log_{10}$ IgG titers at 0, 1, 12, and 24 months post revaccination among HIV-infected children on antiretrovirals who were seronegative at time of revaccination

Table 1

Demographic and clinical characteristics of HIV-infected children on antiretroviral therapy and their caregivers

	No. or median	% or IQR ^I
Child Characteristics		
Age (years)	7.5	5.5 – 9.5
Male	123	53
CD4%	32	27 – 38
CD4% 25	188	81
Plasma HIV RNA (copies/mL)		
<50	141	61
50–999	38	16
1,000	52	23
Age at HIV diagnosis (years)	3.3	1.7 – 4.8
Age at ART ² initiation	3.6	1.9 – 5.3
Years on ART at time of revaccination ³	3.4	1.8 – 4.9
On ART at time of first measles vaccination ⁴	10	10
WHO Stage ⁵		
Not Advanced (I or II)	64	30
Advanced (III or IV)	148	70
Previous measles vaccinations ⁶		
0	4	2
1	223	96
2	5	2
Vitamin A status ⁷		
Severely deficient (RBP ⁸ <0.7umol/L)	7	3
Moderately deficient (RBP 0.7–1.05 umol/L)	52	23
Stunted (length/height-for-age z-score <–2)	54	23
Underweight (weight-for-age z-score <–2)	11	5
Wasted (weight-for-length/height z-score <–2)	1	0.4
BMI ⁹	15.5	14.8 – 16.5
Caregiver Characteristics		
Mother is primary caregiver	190	82
Age	33	30 – 38
Years of completed school	11	8 – 12
Married	149	64
Renting home	199	86
Monthly rent if renting	41	24 – 59
Rooms per household	2	1 – 3
People per household	4	4 – 5

¹ Interquartile range;

² Antiretroviral therapy (ART);

³ Out of 216 with record of ART history;

⁴ Out of 103 with vaccination card and ART history;

⁵ Out of 212 with clinical record history;

⁶ By verbal report or vaccination history card;

⁷ After correction for markers of inflammation;

⁸ Retinol-binding protein (RBP);

⁹ Body Mass Index (BMI) for 184 children 5+ years of age.

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Univariate and multivariate risk factors for measles seropositivity at 24 months post revaccination among HIV-infected children on antiretroviral therapy

Table 2

Child characteristic at time of revaccination	Total N	Seropositive n(%)	RR ¹	95% CI ²	p-value
Demographic					
Age (years)					
<5	44	27 (61)	1	Ref.	
5+	176	106 (60)	0.98	0.75, 1.28	0.89
Sex					
Female	103	67 (65)	1	Ref.	
Male	117	66 (56)	0.87	0.70, 1.07	1.91
Immunologic					
Serostatus at enrollment					
Seronegative	102	26 (25)	1	Ref.	
Seropositive	118	107 (91)	3.56	2.54, 4.99	<0.001
CD4%					
<30	80	38 (48)	1	Ref.	
30	140	95 (68)	1.43	1.10, 1.85	0.007
Plasma HIV RNA (copies/mL)					
<50	135	93 (69)	1	Ref.	
50–999	36	21 (58)	0.85	0.63, 1.14	0.28
1,000	49	19 (39)	0.56	0.39, 0.82	0.002
Years on ART ³					
<1	24	12 (50)	1	Ref.	
1–4.9	132	81 (61)	0.21	0.79, 1.85	0.38
5+	46	33 (72)	1.43	0.92, 2.23	0.11
WHO Stage					
Early (I & II)	64	38 (59)	1	Ref.	
Advanced (III & IV)	140	88 (63)	1.06	0.83, 1.35	0.64
Nutritional					
HFA ⁴ z-score	220	133 (60)	1.06	0.97, 1.17	0.21
Stunting ⁵					

Child characteristic at time of revaccination	Total N	Seropositive n(%)	RR ¹	95% CI ²	p-value
Not stunted	168	101 (60)	1	Ref.	
Stunted	52	32 (62)	1.02	0.80, 1.31	0.85
BMI	175	105 (60)	1.02	0.95, 1.08	0.63
Vitamin A (RBP umol/L) ⁶					
1.06+	162	96 (59)	1	Ref.	
0.7–1.05	50	33 (66)	1.11	0.88, 1.41	0.37
<0.7	7	3 (43)	0.72	0.30, 1.72	0.46
Multivariate Analyses					
	aRR ⁷	95% CI	p-value		
Serostatus at enrollment					
Seronegative	1	Ref.			
Seropositive	3.43	2.45, 4.80	<0.001		
Plasma HIV RNA (copies/mL)					
<50	1	Ref.			
50–999	0.93	0.77, 1.12	0.42		
1,000	0.67	0.51, 0.87	0.003		
Serostatus at enrollment					
Seronegative	1	Ref.			
Seropositive	3.54	2.51, 4.98	<0.001		
CD4%					
<30	1	Ref.			
30	1.02	0.89, 1.18	0.77		

¹ Relative Risk;² Confidence Interval;³ Antiretroviral therapy;⁴ Length/height-for-age z-score;⁵ Stunted defined as length/height-for-age z-score < -2;

Retinol-binding protein, after correction for markers of inflammation;
7 Adjusted Relative Risk.

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Univariate risk factors for measles seroconversion at 24 months post revaccination among HIV-infected children on antiretroviral therapy

Table 3

Demographic	Univariate Analysis			
	Total N	Seroconverted n(%)	RR ¹	95% CI ² p-value
Age (years)				
<5	16	3 (19)	1	Ref.
5+	86	23 (27)	1.43	0.48, 4.22 0.52
Sex				
Female	44	12 (27)	1	Ref.
Male	58	14 (24)	0.89	1.45, 1.73 0.72
Immunologic				
CD4%				
<30%	47	8 (17)	1	Ref.
30%	55	18 (33)	1.92	0.92, 4.03 0.083
Plasma HIV RNA (copies/mL)				
<50	56	22 (39)	1	Ref.
50–999	18	3 (17)	0.42	0.14, 1.26 0.12
1,000	28	1 (4)	0.09	0.01, 0.65 0.017
Years on ART ³				
<1	13	3 (23)	1	Ref.
1–4.9	62	16 (26)	1.12	0.38, 3.31 0.84
5+	17	5 (29)	1.27	0.37, 4.42 0.70
WHO Stage				
Early (I & II)	36	12 (33)	1	Ref.
Advanced (III & IV)	57	13 (23)	0.68	0.35, 1.33 0.27
Nutritional				
HFA ⁴ z-score	102	26 (25)	1.29	0.99, 1.68 0.063
Stunting ⁵				
Not stunted	82	22 (27)	1	Ref.

Univariate Analysis					
	Total N	Seroconverted n(%)	RR ¹	95% CI ²	p-value
Stunted	20	4 (20)	0.75	0.29, 1.93	0.55
BMI	89	23 (26)	1.02	0.85, 1.22	0.87
Vitamin A (RBP umol/L) ⁶					
1.06+	82	22 (27)	1	Ref.	
0.7–1.05	16	4 (25)	0.93	0.37, 2.35	0.88
<0.7	4	0 (0)	n/a	n/a	n/a

¹Relative Risk;
²Confidence Interval;
³Antiretroviral therapy;
⁴Length/height-for-age z-score;
⁵Stunted defined as length/height-for-age z-score < -2;
⁶Retinol-binding protein, after correction for markers of inflammation.

Table 4

Multivariate risk factors for measles seroconversion at 24 months post revaccination among HIV-infected children on antiretroviral therapy

	Multivariate Analyses		
	aRR ¹	95% CI ²	p-value
CD4%			
<30%	1	Ref.	
30%	2.00	0.97, 4.13	0.060
HFA ³ z-score	1.30	1.02, 1.66	0.036
Plasma HIV RNA (copies/mL)			
<50	1	Ref.	
50–999	0.46	0.15, 1.39	0.17
1,000	0.09	0.01, 0.67	0.018
HFA z-score	1.20	0.96, 1.51	0.11

¹Adjusted Relative Risk;

²Confidence Interval;

³Length/height-for-age z-score.