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Immunity Following Childhood Vaccinations in Perinatally HIV-Exposed Children with and without HIV Infection in Latin America

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Abstract

Background—Perinatally HIV-infected (PHIV) children are at risk for undervaccination and poor vaccine response at four years of age. Childhood vaccine coverage and immune response were compared between PHIV and HIV-exposed uninfected (HEU) children in Latin America and the Caribbean.

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Supplemental Digital Content List:

Supplemental Table 1 (.docx file)

Methods—PHIV and HEU children were enrolled prospectively at fifteen sites from 2002–2009. Full vaccination by age four years was defined as: three hepatitis B virus (HBV) vaccine doses; four tetanus toxoid-containing vaccine doses; three doses of *Haemophilus influenzae* type b (Hib) vaccine by age 12 months or ≥1 dose given after age 12 months; one measles-containing vaccine dose; one rubella-containing vaccine dose. Immunity was defined by serum antibody titer. Fisher's exact test (for categorical measures) and t-test (for continuous measures) were used for comparisons.

Results—Among 519 children seen at age four years, 191 had serum specimens available (137 PHIV, 54 HEU). Among those with specimens available, 29.3% initiated combination antiretroviral therapy (cART) <12 months of age, 30.9% initiated at ≥12 months of age, and 39.8% had not received cART by the time they were seen at four years of age.

At four years of age, 59.9% were on PI-containing cART (cART/PI), and 20.4% were on no ARV. PHIV children were less likely than HEU children to be fully vaccinated for tetanus (55.5% vs. 77.8%, p=0.005) and measles and rubella (both 70.1% vs. 94.4%, p<0.001). Among those fully vaccinated, immunity was significantly lower among PHIV than HEU for all vaccines examined: 20.9% vs. 37.8% for HBV (p=0.04), 72.0% vs. 90.5% for tetanus (p=0.02), 51.4% vs. 68.8% for Hib (p=0.05), 80.2% vs. 100% for measles (p<0.001) and 72.9% vs. 98.0% for rubella (p<0.001) vaccine, respectively.

Conclusions—Compared to HEU, PHIV children were significantly less likely to be immune to vaccine-preventable diseases when fully vaccinated. Strategies to increase immunity against vaccine-preventable diseases among PHIV require further study.

Keywords

Pediatric HIV infection; vaccination; immunity; Latin America

INTRODUCTION

Perinatally HIV-infected (PHIV) and HIV-exposed uninfected (HEU) children are vulnerable to vaccine-preventable infectious diseases, which can result in high mortality and morbidity, especially in the early years of life. This risk may be compounded by missed opportunities for recommended immunizations in PHIV, despite specific immunization guidelines for HIV-infected children (1, 2, 3), perhaps because healthcare providers may be unaware of the recommendations or concerned that vaccination poses greater risks in this population. In a previous study of Latin American and Caribbean PHIV and HEU children enrolled in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI), the rates of complete vaccination of children at age 24 months varied from 43.5% to 74.5% in the PHIV group and 74.2% to 94.2% in the HEU group with PHIV children being significantly less likely to be vaccinated for all vaccines examined (4).

In addition to suboptimal vaccination rates, PHIV children may not respond serologically with the same magnitude or durability as children without HIV infection. Before the introduction of combination antiretroviral therapy (cART), the development of protective antibody levels following primary immunization in asymptomatic or symptomatic HIV-

infected children was 40–100% for tetanus and diphtheria vaccines, 25–50% for hepatitis B (HBV) vaccine, and 37–86% for *Haemophilus influenzae* type b (Hib) conjugate vaccine (5). Even in children who received cART, the prevalence of measles and rubella antibodies after primary immunization was only 38% to 42% (6, 7).

The objective of the current study was to compare coverage rates between PHIV and HEU children in the NISDI cohort at age 4 years for routine childhood vaccinations (HBV, tetanus, Hib, measles, and rubella) and compare cohort serologic immune responses between PHIV and HEU who had received these vaccines according to standard recommendations by age four years. The analysis examines the subset of patients included in the prior analysis who had serum specimens available for testing at age 4 years, the time point where the largest number of specimens were available for the comparison between PHIV and HEU children.

MATERIALS AND METHODS

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development International Site Development Initiative (NISDI) enrolled PHIV and HEU children into two prospective cohort studies conducted at fifteen sites in Latin America and the Caribbean from 2002 to 2009. Detailed protocol information has been published (8). In brief, from 2002–2007 the Pediatric protocol enrolled PHIV infants, children, and adolescents (up to 21 years old) and HEU children (up to 12 months old) at sites in Brazil, Mexico, Argentina, Peru, and Jamaica. The Pediatric Latin American Countries Epidemiologic Study (PLACES) was an extension of the prior Pediatric protocol that only enrolled PHIV. From 2008 to 2011, PLACES enrolled PHIV children <6 years of age at sites in Brazil, Mexico, and Peru. Both protocols had the primary objective to describe the demographic, clinical, immunologic, and virologic characteristics of enrolled HIV-exposed and/or infected children. The forms and procedures used to collect vaccination information included in this analysis were identical across the two protocols. The protocols were approved by the ethical review boards of each participating clinical site, by the sponsoring institution (NICHD), the data management and statistical center (Westat), the Peruvian Ministry of Health and the Brazilian National Ethics Committee. Informed consent was obtained from parents or legal guardians of all participants.

Information was collected from all enrolled children, including: gestational age, birth weight, and vaccinations received from birth up to the age of enrollment. The vaccination history up to enrollment was obtained through retrospective review of medical records. All children were clinically evaluated in a standardized fashion every six months, including laboratory assessments (CD4+ T-lymphocyte [CD4] percent, CD4 counts and HIV RNA viral load (VL), for PHIV), use of cART (defined as regimen of at least 3 three antiretroviral drugs), and any additional vaccinations.

HIV infection was based on reactive HIV tests on two different occasions (virologic tests if under age 18 months, virologic and/or antibody tests if age ≥18 months). HEU children had negative HIV virologic testing at ages ≥ one month and ≥ four months or repeatedly non-reactive HIV antibody testing at age ≥ six months. Eligibility for this analysis was limited to

HEU and PHIV children who had serum specimens available at their four-year-old visit (48 months of age +/− 3 months). Only vaccinations received at least 14 days prior to the date of serum specimen collection were considered in determining children's vaccination status.

Children were considered fully vaccinated for a specific vaccine if they had received the recommended number of doses for that vaccine, and the doses followed minimum age and minimum interval guidelines, according to World Health Organization recommendations (9). Fully vaccinated at four years of age was defined for each vaccination as follows: three doses of HBV vaccine; four doses of any tetanus toxoid-containing vaccine; three doses of Hib vaccine by 12 months of age or at least one dose of Hib given after 12 months of age; one dose of measles-containing vaccine; and one dose of rubella-containing vaccine.

Diasorin testing kits (Saluggia, Italy) were used to measure antibody for HBV (ETI-AB-AUK-3) and rubella (ETI-RUBEK-G PLUS), with estimates of antibody titers calculated from calibration curves for HBV based on five calibrators (0, 10, 100, 500 and 1000 IU/mL) and rubella based on four calibrators (10, 25, 50 and 200 IU/mL). Tetanus antibodies were measured by in-house double antigen ELISA as described by Kristiansen et al. (10). Hib IgG antibodies were measured by indirect ELISA (11). Measles IgG antibodies were measured by indirect ELISA as previously described (12). All the tests were performed at the same laboratory.

A child was considered immune at four years of age for each disease as follows: HBV surface antibody titer ≥10 IU/L (13), tetanus antibody titer ≥ 0.1 IU/mL (14), Hib antibody titer ≥1.0 μg/mL (15), measles antibody titer ≥0.120 IU/mL (16), and rubella antibody titer ≥10 IU/mL (17).

Statistical Methods

Descriptive statistics (frequencies, proportions, means, standard deviations [SD], medians and ranges) were used to summarize characteristics of the study population. Fisher's exact test was used to evaluate relationships between categorical-scaled characteristics and HIV status, while the Student's t-test was used to examine associations with continuous-scaled characteristics. The association of vaccination status (fully vaccinated vs. not fully vaccinated) with HIV status was examined for each vaccine at four years of age using Fisher's exact test. Among those fully vaccinated, the associations of serologic immunity with HIV status and (for PHIV only) with HIV-1 viral load (VL), CD4% and timing of initiation of cART were also examined using Fisher's exact test. The geometric mean antibody titers were described by HIV status for each vaccine, as was the median days from last vaccine dose comparing PHIV to HEU children separately for those who were immune and those non-immune (compared by Nonparametric Kruskal-Wallis test).

All analyses were conducted using the SAS statistical software, version 9.2 or later (SAS Institute Inc. Cary, NC), with an alpha level of <0.05 used to identify significant associations.

RESULTS

Among the 1926 children enrolled in the NISDI Pediatric protocols, 1293 were enrolled prior to age four years, of which 519 had at least one visit at 48±3 months of age; 314 were PHIV and 205 were HEU. Of these, 43.6% (137/314) of PHIV children and 26.3% (54/205) of HEU had serum specimens available for testing at four years of age and therefore were eligible for this analysis (62 enrolled in Pediatric protocol only, 119 in PLACES only, 10 in both protocols). Children with serum specimens available (i.e., included in the analysis) were similar to those without specimens available (i.e., excluded from the analysis) on the basis of general demographic and clinical characteristics (see table, Supplemental Digital Content 1). PHIV children were significantly older at enrollment than HEU children (mean of 34.7 vs. 4.4 months, respectively, $p<0.001$), reflecting the differing enrollment criteria of the protocols (Table 1). PHIV subjects did not differ from HEU in gestational age at birth, gender, or BMI at four years of age ($p>0.5$). For descriptive purposes, HIV-related characteristics of PHIV children are also shown in Table 1. At the four year visit, 65% of PHIV children showed no immunosuppression, most (59.9%) were receiving protease inhibitor-containing cART, and nearly half (49.6%) had viral loads less than 500 copies/mL. At age four years, significantly ($p<0.01$) smaller proportions of PHIV than HEU children were fully vaccinated for tetanus, measles, and rubella (Table 2).

Subsequent analyses were restricted to those who were fully vaccinated by age four years. Among fully vaccinated children, serologic status at the four-year visit for each vaccine-preventable disease tested was significantly associated with the children's HIV status (Table 3). Compared to HEU children, PHIV children were less likely to be immune to HBV (20.9% vs 37.8%; $p=0.04$), tetanus (72.0% vs 90.5%; $p=0.02$), and Hib (51.4% vs 68.8%; 0.05). Only 80.2% of PHIV children were immune to measles, while all HEU children who received at least one dose of measles-containing vaccine by age four years were immune ($p<0.001$) with similar results for rubella (72.9% vs 98.0 %; $p<0.001$).

Among those considered serologically immune, the geometric mean antibody titer was significantly lower for PHIV than HEU subjects for tetanus, measles and rubella, but not for HBV and Hib (Table 3). Median time from last vaccine dose was shorter for PHIV than HEU children, but only significantly less for HBV (immune and nonimmune, $p<0.001$), Hib (non-immune, $p<0.001$) and tetanus (immune, $p<0.036$) vaccination.

The association of viral load (VL) and CD4% with serologic immunity was examined among PHIV children (Table 4). VL (<1000 vs. ≥1000 copies/mL) and CD4% (≥25% vs. <25%) measured at four years of age were not associated with serologic immunity to most vaccines; however, a higher proportion of those with VL<1000 copies/mL were immune to tetanus than among those with VL >1000 copies/mL (85.1% vs. 50.0%, $p<0.01$). Serologic immunity was associated with timing of cART initiation only for HBV ($p=0.049$) (Table 5). A larger proportion of children who started cART prior to 12 months of age were immune to HBV (31.9%), compared to those initiating cART at or after 12 months of age (14.9%) and those that did not initiate cART (6.2%).

DISCUSSION

In this cohort of Latin American children significantly smaller proportions of PHIV than HEU children were fully vaccinated for tetanus, measles, and rubella by four years of age. Among fully vaccinated children, PHIV children were significantly less likely to have serologic evidence of immunity at four years of age than HEU children for all vaccine-related diseases tested. With the exception of tetanus, VL and CD4% at four years of age were not associated with serologic immunity among PHIV children. Serologic immunity was associated with timing of cART initiation for HBV vaccine, with a larger proportion of children initiating cART prior to 12 months of age having seroprotection at age 4 years. Previous studies had already demonstrated that early cART initiation permits better immune response to vaccines (18) and maintenance of the memory B cells (19).

A protective level of an anti-tetanus antibody is a major factor determining protection against this disease. Among those fully immunized, 72% of PHIV children in our cohort had protective immunity at four years of age. Other studies have reported that a significant proportion of HIV-infected children are not initially protected against tetanus and many who mount an initial immune response end up experiencing waning antibody response long-term. A study of 90 newly-diagnosed, HIV-infected Kenyan children (median age at enrollment 4.9 years, all WHO Stage III and IV, with a history of prior tetanus vaccination) not yet started on ART found 78% had protective titers of tetanus antibodies (20). Among 24 HIV-infected American children (not on ART) that received four (74% were protected) or five (54% were protected) doses of DPT vaccine, declining antibody levels were observed on 10 months follow-up (21).

There are limited studies about the protection against invasive Hib diseases in HIV-infected children (22). In our study, only 79.6% of PHIV children were fully vaccinated and among those fully vaccinated, 48.6% did not have protective Hib antibody levels at four years of age. The proportion of unprotected children observed in 18 American HIV-infected children treated with cART was 22%, even though they were previously immunized with one to four doses of conjugate Hib vaccine; however, their results could be explained by the different timing of evaluation between immunization and serologic testing (median age 7 years) (23).

In our study, the rate of protective immunity was lowest for HBV - 37.8% vs. 20.9% for HEU and PHIV, respectively - with HEU children significantly more likely to be immune ($p=0.04$). HBV serologic immunity was associated with timing of cART initiation ($p=0.049$), with a larger proportion of immune response among children initiating early cART (< 12 months of age). Seroprotection following the HBV vaccine series is less likely in untreated HIV-infected children – even after subsequent immune reconstitution with cART - when compared with HIV-uninfected children (24, 25), and many vertically HIV-infected children who respond to HBV reimmunization after cART lose seroprotection within 3 years (26,27).

The proportion of fully-vaccinated, PHIV children found to be immune to measles and rubella at four years (80.2% and 72.9%, respectively) was significantly lower than HEU children (100% and 98.0%, respectively). Our findings are similar to a Brazilian study that

demonstrated an 80% seroconversion rate for rubella vaccine among 15 HIV-infected children on cART after MMR vaccination at 15 months of age (28). In the Pediatric Amsterdam Cohort of 59 HIV-1 infected children who started treatment with cART at a median age of 4.3 years and reported to be immunized with MMR vaccine, only 35 (63%) children had specific antibodies against measles and 45 (80%) against rubella (29); moreover 40% of the measles seropositive and 11% of the rubella seropositive children lost their specific antibodies during a period of 192 weeks follow-up. A US American study of 428 PHIV and 221 HEU children aged 7–15 years observed seroprotection of 57% (PHIV) vs. 99% (HEU) for measles, 65% vs. 98% for rubella and 59% vs. 97% for mumps (30).

High levels of immunization coverage caused endemic transmission of measles to end in the Americas by 2002. Recent measles outbreaks in the United States and Brazil suggest that immunization rates in some areas have dropped below levels needed to prevent the spread of cases imported into the Americas (28). These outbreaks could allow measles and other vaccine-preventable diseases to spread particularly in the immunocompromised population.

Limitations of this study that was based on the review of medical records include the possibility that records may not be complete, and since subjects were enrolled from four countries, the dosing schedules and the vaccine products themselves could be different. However, we included only children with evidence of full vaccination with proper dosing schedules in the determination of immunity to mitigate these potential issues. In addition, this study benefits from systematic data collection using standardized forms and training and large sample size for assessing statistical associations, although for some of comparisons the sample size is small. One additional strength is that the measure of antibodies in all samples have been performed by the same laboratory, which could minimize intra-assay, interassay, and inter-laboratory variabilities.

HIV-infected children may experience failure to receive appropriate vaccinations, poorer immunologic response, and accelerated loss of antibodies after immunization. Complete and timely vaccination of PHIV according to the immunization schedule recommended for this group is critical. In communities with high immunization coverage levels, the risk could be reduced by herd immunity, but outbreaks of infectious disease like measles and rubella can occur.

Knowledge of waning immunity to HBV, tetanus, Hib, measles, and rubella in HIV-infected and HIV-exposed uninfected children, as well as the need for booster doses, is not well studied and larger studies are warranted (31–34).

Conclusions

Even once fully vaccinated, significantly lower proportions of PHIV children are immune to vaccine-preventable diseases. Strategies to improve routine PHIV vaccine coverage and to increase PHIV immunity following vaccination require further study. In addition, maintenance of immunity should be investigated in this high-risk group. This is especially important if we consider the recent measles outbreaks in different parts of the Americas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic characteristics of children by HIV status

Characteristic	PHIV N (%)	HEU N (%)	P-value[1]
Country:			
Argentina	2 (1.5)	15 (27.8)	<0.001
Brazil	85 (62.0)	39 (72.2)	
Mexico	22 (16.1)	0	
Peru	28 (20.4)	0	
Gestational age at birth:			
<37	10 (12.8)	4 (8.7)	0.57
≥ 37	68 (87.2)	42 (91.3)	
Missing	59	8	
Gender:			
Female	56 (40.9)	24 (44.4)	0.74
Male	81 (59.1)	30 (55.6)	
Age at enrollment (months):			
Mean (SD)	34.7 (11.3)	4.4 (3.8)	<0.001
Median	36.0	4.0	
Range	5–51	0–11	
BMI at four years of age:			
<−2 SD	2 (1.5)	0	0.89
−2 SD to +2SD	122 (89.0)	48 (88.9)	
>+2 SD	13 (9.5)	6 (11.1)	
Immunologic status (CD4 count) at age four years:			
No suppression (≥1000 cells/mm^3)	89 (65.0)	44 (81.5)	0.05
Moderate (500–999 cells/mm^3)	42 (30.6)	10 (18.5)	
Severe (<500 cells/mm^3)	6 (4.4)	0	
ARV prescribed at age four years:			
cART/PI	82 (59.9)	NA	
cART/NNRTI	24 (17.5)		
No cART	3 (2.2)		
No ARV	28 (20.4)		
CDC classification at age four years:			
N	11 (8.0)	NA	
A	34 (24.8)		
B	38 (27.7)		
C	54 (39.4)		

Characteristic	**PHIV N (%)**	**HEU N (%)**	**P-value[1]**
Viral Load (copies/mL) at age four years:			
<500	68 (49.6)	NA	
500–10,000	25 (18.2)		
10,000<100,000	29 (21.2)		
≥100,000	15 (11.0)		

[1] P-values obtained using Fisher's exact test for categorical characteristics and the t-test for continuous measures.

PHIV- Perinatally HIV-infected; **HEU**- HIV-exposed uninfected; **BMI**-Body Mass Index; **ARV**- antiretroviral treatment; **cART**- ARV regimen with at least 3 antiretroviral drugs; **cART/PI**- cART with Protease inhibitor drug; **cART/NNRTI**-cART with Non-Nucleoside Reverse Transcriptase Inhibitors drug.

Table 2

Vaccination status among PHIV and HEU children at four year visit

Vaccine	Fully vaccinated[1]	PHIV n (%)	HEU n (%)	P-value[2]
HBV	Yes	110 (80.3)	45 (83.3)	0.69
	No	27 (19.7)	9 (16.7)	
Tetanus	Yes	76 (55.5)	42 (77.8)	0.005
	No	61 (44.5)	12 (22.2)	
Hib	Yes	109 (79.6)	48 (88.9)	0.15
	No	28 (20.4)	6 (11.1)	
Measles	Yes	96 (70.1)	51 (94.4)	<0.001
	No	41 (29.9)	3 (5.6)	
Rubella	Yes	96 (70.1)	51 (94.4)	<0.001
	No	41 (29.9)	3 (5.6)	

[1] Fully vaccinated at the four year visit for the different vaccines was defined as: three doses of Hepatitis B virus (HBV) vaccine; four doses of any tetanus toxoid-containing vaccine; three doses of *Haemophilus influenzae* (Hib) vaccine prior to 12 months of age or at least one dose after 12 months of age; one dose of any measles-containing vaccine; one dose of any rubella-containing vaccine. Only vaccinations received at least 14 days prior to the date of serum specimen collection were considered in determining children's vaccination status.

[2] P-values obtained using Fisher's exact test.

Table 3

Serologic status, geometric mean antibody titers and timing of serology by HIV status among those fully vaccinated

Vaccine	Immunity				Geometric mean titer			Median days from last vaccine dose		
		N (%)								
	Serologic immunity[1]	PHIV	HEU	P-value[2]	PHIV	HEU	P-value[3]	PHIV	HEU	p-value[3]
HBV	Yes	23 (20.9)	17 (37.8)	0.04	76.2	33.9	0.03	882	1255	<0.001
	No	87 (79.1)	28 (62.2)					1221	1290	<0.001
Tetanus[4]	Yes	54 (72.0)	38 (90.5)	0.02	0.42	0.66	0.03	917	956	0.036
	No	21 (28.0)	4 (9.5)					716	956	0.10
Hib	Yes	56 (51.4)	33 (68.8)	0.05	4.33	2.85	0.14	954	1066	0.15
	No	53 (48.6)	15 (31.2)					1085	1250	<0.001
Measles	Yes	77 (80.2)	51 (100.0)	<0.001	1.90	6.93	<0.001	1021	1037	0.60
	No	19 (19.8)	0 (0.0)					1045	–	–
Rubella	Yes	70 (72.9)	50 (98.0)	<0.001	52.19	57.8	0.01	1020	1033	0.47
	No	26 (27.1)	1 (2.0)					1029	1093	0.35

[1] Immunity defined as: hepatitis B surface antibody titer ≥10 IU/L, tetanus antibody titer ≥0.1 IU/mL, Hib antibody titer ≥1.0 μg/mL, measles antibody titer ≥0.120 IU/mL, rubella antibody titer ≥10 IU/mL.

[2] P-values obtained using Fisher's exact test.

[3] Nonparametric Kruskal-Wallis test.

[4] One PHIV child missing serologic result for tetanus.

Table 4

Immunity among fully vaccinated PHIV children by viral load and CD4% at four year old visit

Vaccine	Serologic immunity[1]	Viral load (VL) at 4-year-old visit				CD4% at 4-year-old visit			
		N	<1000 copies/mL N (%)	≥1000 copies/mL N (%)	P- value[2]	N[3]	CD4% ≥25% N (%)	CD4% <25% N (%)	P-value[2]
HBV	Yes	23	15 (24.6)	8 (16.3)	0.35	22	19 (25.0)	3 (13.0)	0.27
	No	87	46 (75.4)	41 (83.7)		77	57 (75.0)	20 (87.0)	
Tetanus[4]	Yes	54	40 (85.1)	14 (50.0)	<0.01	51	41 (74.6)	10 (76.9)	1.0
	No	21	7 (14.9)	14 (50.0)		17	14 (25.4)	3 (23.1)	
Hib	Yes	56	35 (56.4)	21 (44.7)	0.25	52	42 (53.2)	10 (43.5)	0.48
	No	53	27 (43.6)	26 (55.3)		50	37 (46.8)	13 (56.5)	
Measles	Yes	77	47 (81.0)	30 (79.0)	0.80	72	52 (80.0)	20 (95.2)	0.17
	No	19	11 (19.0)	8 (21.0)		14	13 (20.0)	1 (4.8)	
Rubella	Yes	70	45 (77.6)	25 (65.8)	0.24	62	49 (75.4)	13 (61.9)	0.27
	No	26	13 (22.4)	13 (34.2)		24	16 (24.6)	8 (38.1)	

[1] Immunity defined as: hepatitis B surface antibody titer ≥10 IU/L, tetanus antibody titer ≥0.1 IU/mL, Hib antibody titer ≥1.0 μg/mL, measles antibody titer ≥0.120 IU/mL, rubella antibody titer ≥10 IU/mL. Non-immune category includes equivocal results for tetanus and Hib.

[2] P-values obtained using Fisher's exact test.

[3] CD4% obtained from visit prior to serology testing (missing values not shown).

Table 5

Relationship between timing of cART initiation and serologic immunity among fully vaccinated PHIV children

Vaccine	Serologic immunity[1]	N	cART initiated <12 months of age N (%)	cART initiated ≥ 12 months of age N (%)	No cART N (%)	P-value[2]
HBV	Immune	23	15 (31.9)	7 (14.9)	1 (6.2)	0.049
	Not immune	87	32 (68.1)	40 (85.1)	15 (93.8)	
Tetanus[3]	Immune	54	24 (72.7)	25 (75.8)	5 (55.6)	0.521
	Not immune	21	9 (27.3)	8 (24.2)	4 (44.4)	
Hib	Immune	56	27 (57.4)	22 (44.9)	7 (53.8)	0.489
	Not immune	53	20 (42.6)	27 (55.1)	6 (46.2)	
Measles	Immune	77	33 (86.8)	33 (76.7)	11 (73.3)	0.405
	Not immune	19	5 (13.2)	10 (23.3)	4 (26.7)	
Rubella	Immune	70	32 (84.2)	29 (67.4)	9 (60.0)	0.20
	Not immune	26	6 (15.8)	14 (32.6)	6 (40.0)	

[1] Considered immune to disease as follows; hepatitis B titer ≥10 IU/L, tetanus titer ≥ 0.1 IU/mL, Hib titer ≥ 1.0 μg/mL, measles titer ≥ 0.120 IU/mL, rubella titer ≥ 10 IU/mL. Equivocal results considered non-immune for tetanus and Hib.

[2] P- values obtained using Fisher's exact test.

[3] Missing one serologic result for tetanus.