
Immunogenicity of 23-valent pneumococcal polysaccharide vaccine in children with human immunodeficiency virus undergoing highly active antiretroviral therapy

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Background: The 23-valent pneumococcal polysaccharide vaccine (23PSV) has been recommended for children infected with human immunodeficiency virus (HIV); however, the efficacy of this vaccination in HIV-infected children undergoing highly active antiretroviral therapy (HAART) has not been studied.

Objective: To study the immunogenicity and immunologic protection of 23PSV in HIV-infected children after stable HAART.

Methods: Serotype-specific IgG antibodies to 12 pneumococcal capsular polysaccharides were analyzed before and after 23PSV vaccination in 41 HIV-infected children undergoing HAART and compared with 95 HIV-negative control children. Seropositivity, clinical protection, and additional clinical protection from 23PSV were calculated based on serotype specific IgG antibody levels and on the known incidence of these serotypes for causing invasive disease.

Results: Children with HIV infection undergoing HAART developed a significant increase in specific IgG levels to *Streptococcus pneumoniae* after 23PSV vaccination (0.95 vs 1.84 $\mu\text{g/mL}$, $P < .001$). The HIV-infected children with CD4⁺ cell counts of 25% or higher at the time of vaccination developed a higher additional clinical protection gain from 23PSV vaccination than did children with a lower percentage of CD4⁺ cells.

Conclusions: HIV-infected children undergoing stable HAART develop a significant immunologic response to 23PSV, especially those with higher T-cell counts and lower viral loads at the time of vaccination.

Ann Allergy Asthma Immunol. 2004;92:558–564.

INTRODUCTION

Streptococcus pneumoniae is the leading bacterial cause of bacteremia, meningitis, pneumonia, and sinusitis in children.¹ The risk and morbidity of invasive pneumococcal disease are much higher in persons infected with human immunodeficiency virus (HIV) and especially in children.^{1,2} Excessive use of antibacterial agents appears to contribute to the rapidly increasing prevalence of antibiotic-resistant *S pneumoniae*, resulting in fewer effective therapeutic agents.³

To control pneumococcal disease, the American Academy of Pediatrics has recommended vaccination of HIV-infected children with 23-valent pneumococcal polysaccharide vaccine (23PSV), as well as heptavalent pneumococcal conjugate vaccine (PCV7).⁴ Pneumococcal conjugate vaccines are considered safe and immunogenic when given to HIV-infected children younger than 2 years^{5,6}; however, the benefit of conjugate vaccines for older HIV-infected children has not been documented. For older children, 23PSV may offer greater advantages than PCV7 due to the lower cost and

expanded serotype coverage for invasive pneumococcal disease (88.2% vs 57.2%).⁷ However, in HIV-infected persons who were not being treated with HAART, 23PSV immunization resulted in a lack of clinical efficacy or poorer immunogenic response.^{5,8,9}

Currently, most HIV-infected children in developed countries are receiving HAART. The treatment has been shown to be effective and has led to immune reconstitution and better responses to vaccinations.^{10–12} Therefore, we studied the immunogenicity and immunologic protection of 23PSV in HIV-infected children after stable HAART compared with non-HIV-infected children.

METHODS

The study was approved by the institutional review board and was performed at the Pediatric HIV Clinic of All Children's Hospital/University of South Florida, St Petersburg, between 1999 and 2002.

Subjects

Subjects were children 2 to 15 years of age who were not taking immunosuppressive medication and who had received no live vaccines 3 months previously, no intravenous immunoglobulin infusion 6 months previously, and no 23PSV vaccination 5 years previously. None had received PCV7 vaccination.

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This work was supported by a grant from the Eleanor Naylor Dana Charitable Trust.

Received for publication September 10, 2003.

Accepted for publication in revised form November 14, 2003.

HIV-Infected Subjects

The HIV-infected subjects included 41 perinatally HIV-infected children undergoing stable HAART, consisting of 3 or more antiretroviral medications, 1 of which was a nonnucleoside reverse transcriptase inhibitor, a protease inhibitor, or a potent nucleoside reverse transcriptase inhibitor (abacavir). For 6 months before the study, subjects could have no change in treatment regimen, no new acquired immunodeficiency virus-defining events, no change in Centers for Disease Control and Prevention (CDC) category, and stable HIV viral loads and CD4⁺ T-cell counts.

Control Subjects

Control subjects included 95 non-HIV-infected children, with no history warranting immunological evaluation.¹³ These children were thoroughly evaluated by pediatric immunologists for any evidence of immunodeficiency. Laboratory evaluation included complete white blood cell count, immunoglobulin panel (IgG, IgA, IgM, and/or IgE), total complement hemolysis (CH₅₀), T- and B-lymphocyte subset enumeration, specific antibodies to previous protein vaccinations (diphtheria and tetanus), and HIV antibody. Further immunologic evaluations were performed on selected individuals as appropriate. Any child with abnormal immune evaluation was excluded.

The 23PSV (polyvalent-PNEUMOVAX* 23, Merck & Co Inc, West Point, PA), containing 23 pneumococcal capsular types, was given by 0.5-mL injection intramuscularly into the anterolateral mid thigh. Venous blood samples were collected before 23PSV vaccination and at 1 to 3 months after vaccination to be analyzed for specific IgG against pneumococcal capsular polysaccharides of the 12 most prevalent pneumococcal serotypes. The antibody titers before and after 23PSV vaccination were determined by enzyme-linked immunosorbent assay (ELISA) per manufacturing protocol (ELISA plates and reagents were from IBT Reference Laboratory, Lenexa, KS). Serum samples were preabsorbed at 1:200 dilution with lyophilized cell wall polysaccharide to remove pneumococcal cell wall polysaccharide and to enhance the specificity of the assay for functional antibodies to the capsule. Each sample was analyzed in duplicate; the coefficient of variation was less than 12%. Immunoglobulin profiles were analyzed by nephelometry. Lymphocyte subset analysis was performed with whole blood samples using flow cytometry, and plasma HIV-1 RNA levels were quantified by polymerase chain reaction (Amplicor Monitor HIV-1 RNA Kit, Roche Diagnostic System, Somerville, NJ).

Statistical Analysis

Because the response to 23PSV may be age dependent, subjects were divided into 2 age groups, 2 to 6 years and 7 to 15 years.¹⁴ The geometric mean concentrations (GMCs) of specific IgG against pneumococcal capsular polysaccharide and clinical protection against *S pneumoniae* were analyzed before and after 23PSV vaccination in HIV-infected subjects and controls, as well as between HIV and control groups. An

adequate seropositivity for each pneumococcal serotype was determined by a specific IgG level of 1.8 $\mu\text{g/mL}$ or higher. Clinical protection against *S pneumoniae* was defined as the likelihood that a subject was protected against various strains of *S pneumoniae* based on their seropositivity to each *S pneumoniae* serotype and on the incidence of that pneumococcal serotype for causing invasive pneumococcal disease in the United States as outlined in a large epidemiologic study performed in 1995 to 1998.⁷ Incidence of invasive pneumococcal disease, defined by isolation of *S pneumoniae* from a normally sterile site (eg, blood, cerebrospinal fluid), used for the calculation of clinical protection in this study was as follows: serotype 1, 3.6% of total invasive pneumococcal diseases; serotype 3, 3.4%; serotype 4, 12.4%; serotype 6B, 6.6%; serotype 7F, 4.0%; serotype 9V, 9.4%; serotype 12F, 4.8%; serotype 14, 12.5%; serotype 18C, 5.0%; serotype 19F, 4.4%; and serotype 23F, 6.9%; these 11 serotypes accounted for 73.0% of the incidence of invasive pneumococcal disease in children older than 2 years. Serotype 8 was not included in the clinical protection calculation due to its low incidence. Clinical protection of a subject was defined as Σ (incidence of each serotype with a specific IgG level $\geq 1.8 \mu\text{g/mL}$ in that subject). Additional clinical protection gain from 23PSV vaccination was defined as clinical protection after 23PSV vaccination minus clinical protection before 23PSV vaccination.

Log-transformed values for antibody concentration before and after 23PSV vaccination were used to minimize the effect of a few high values and to calculate the geometric mean. The independent sample *t* test and Mann-Whitney *U* test were used to compare controls and HIV-infected children for normal distribution and nonparametric data, respectively. The paired sample *t* test and Wilcoxon signed rank test were used to compare normal distribution and nonparametric data before and after 23PSV vaccination for each group, respectively. A χ^2 test was used for analysis of the categorical variables. Two-sided tests were used, and $P < .05$ was considered statistically significant. All analyses were performed using SPSS for Windows, version 10.0 (SPSS Inc, Chicago, IL).

RESULTS

The study population consisted of 136 children, 41 HIV infected and 95 non-HIV infected, all immunized with 23PSV (Table 1). Of the HIV-infected subjects, 16 were between ages 2 and 6 years (mean, 4.6 years; SD, 1.56 years) and 25 were between ages 7 and 15 years (mean, 10.9 years; SD, 2.36 years). Average time following the HAART regimen was 19.9 months (SD, 11.9 months). Of the non-HIV-infected subjects, 77 were between ages 2 and 6 years (mean, 3.7 years; SD, 1.49 years) and 18 were between ages 7 and 15 years (mean, 9.6 years; SD, 2.57 years). As shown in Table 1, there was no difference in age, sex, or race between HIV-infected subjects and controls. The HIV-infected subjects had

Table 1. Demographic Data of HIV-Infected Children and Non-HIV-Infected Controls at the Time of 23PSV Vaccination

Demographic	HIV-infected children	Controls	P value*
Total No. of subjects	41	95	
No. of younger children (2–6 y)	16	77	
Mean $\pm$ SD age, y	4.6 $\pm$ 1.56	3.7 $\pm$ 1.49	.07
No. of older children (7–15 y)	25	18	
Mean $\pm$ SD age, y	10.9 $\pm$ 2.36	9.6 $\pm$ 2.57	.08
Sex, %			
Male	17 (41.5)	48 (50.5)	.35
Female	24 (58.5)	47 (49.5)	
Race, %			
White	23 (56.1)	70 (73.7)	.04
Black	13 (31.7)	18 (18.9)	.12
Others	5 (12.2)	7 (7.4)	.31
CDC category, No. (%)		NA	
1	9 (22.0)		
2	13 (31.7)		
3	19 (46.3)		
A	24 (58.5)		
B	9 (22.0)		
C	8 (19.5)		
Antiretroviral therapy†		NA	
Regimen contains abacavir, No. (%)	4 (9.8)		
Regimen contains NNRTI, No. (%)	17 (41.4)		
Regimen contains PI, No. (%)	25 (61.0)		
Duration undergoing the therapy, mean $\pm$ SD, mo‡	19.9 $\pm$ 11.9		
Immunoglobulin levels, mean $\pm$ SD, mg/dL			
IgG	1,898 $\pm$ 872.2	741 $\pm$ 296.3	<.001
IgA	267 $\pm$ 230.1	92 $\pm$ 69.3	<.001
IgM	160 $\pm$ 106.2	102 $\pm$ 42.4	.001
CD4 ⁺ T-cell count			
Total, mean $\pm$ SD	962 $\pm$ 510.4	1341 $\pm$ 643.9	.002
Percentage, mean $\pm$ SD, /mm ³	31.9 $\pm$ 10.2	39.1 $\pm$ 8.9	<.001
Subjects with $\geq$ 25%, No. (%)	32 (78.0)	95 (100)	
Viral load			
Total mean $\pm$ SD, copies/mL	11,925 $\pm$ 24,483	NA	
Subjects with <50 copies/mL, No. (%)	16 (36.6)	NA	
Subjects with >30,000 copies/mL, No. (%)	5 (12.2)	NA	

Abbreviations: 23PSV, 23-valent pneumococcal polysaccharide vaccine; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; NA, not applicable; NNRTI, nonnucleoside analog reverse transcriptase inhibitor; PI, protease inhibitor.

* Comparison among patients and controls by *t* test and Mann-Whitney *U* test.

† All HIV-infected subjects received at least 3 antiretroviral medications; 5 subjects received more than 1 PI or NNRTI.

‡ Time from starting a stable highly active antiretroviral therapy regimen to the time of 23PSV vaccination.

higher immunoglobulin levels and lower CD4⁺ T-cell counts and percentages when compared with control subjects.

Baseline Antibody to *S pneumoniae* Serotypes Before 23PSV Vaccination

Before 23PSV administration, both HIV-infected subjects had low titers and were not different from controls (GMC, 0.95 vs 0.80 μ g/mL; *P* = .20; Table 2). When the data were analyzed by each specific serotype, only a slight difference was found. In the younger subjects, pre-23PSV titers of serotypes 3 and 19F were higher in the HIV group and the serotype 7F titer was higher in the control group. In the older subjects, the pre-23PSV titer of serotype 3 was higher in the

HIV-infected group. Antibody to serotype 14 at baseline was highest in both the HIV-infected and control groups.

Antibody Response of Children After Pneumococcal Vaccine

After vaccination, both HIV-infected and control subjects produced a significant increase in titers (Table 2). Younger HIV-infected subjects produced no significant increase in post-23PSV titer in serotypes 6B, 14, 19F, and 23F, and older HIV-infected subjects produced no increase in serotypes 6B and 14. On comparing the HIV-infected and control subjects, the average post-23PSV titer was significantly lower in the HIV-infected subjects (GMC, 1.84 vs 2.77 μ g/mL; *P* <

Table 2. Geometric Mean Concentration of IgG Antibody to Specific Serotype of *Streptococcus pneumoniae* before and after 23PSV Vaccination

Serotype	Geometric mean concentration, $\mu\text{g/mL}$					
	HIV-infected children			Controls		
	Pre-23PSV	Post-23PSV	<i>P</i> value*	Pre-23PSV	Post-23PSV	<i>P</i> value*
Younger children (age 2–6 y)						
1	0.55	1.29†	.002	0.74	3.23	<.001
3	1.28†	2.79	.002	0.62	3.96	<.001
4‡	0.40	1.25	<.001	0.67	1.76	<.001
6B‡	0.74	0.92	.37	0.67	1.16	<.001
7F	0.45†	1.69†	.001	0.78	3.82	<.001
8	0.66	2.19†	<.001	0.97	7.66	<.001
9V‡	0.46	1.73†	<.001	0.63	4.44	<.001
12F	0.58	1.11	.02	0.70	1.44	<.001
14‡	1.25	1.86	.20	1.83	2.89	<.001
18C‡	0.51	1.07†	.02	0.40	2.17	<.001
19F‡	0.85†	0.96	.55	0.49	1.15	<.001
23F‡	0.73	1.13†	.09	1.07	2.23	<.001
Older children (age 7–15 y)						
1	1.01	2.47†	<.001	0.96	4.82	<.001
3	1.65†	2.65	.003	0.77	3.91	<.001
4‡	1.20	1.91	.003	0.75	2.47	.003
6B‡	0.95	1.38	.06	0.98	2.19	.007
7F	1.78	2.79†	.002	1.42	6.21	<.001
8	1.35	4.41†	<.001	1.47	9.63	<.001
9V‡	0.85	2.19†	<.001	0.70	4.47	<.001
12F	1.30	1.89	.04	1.11	2.44	.002
14‡	2.55	2.37†	.47	2.84	5.52	.005
18C‡	0.81	1.73	.01	0.57	3.08	<.001
19F‡	1.28	1.67	.04	1.12	2.56	.005
23F‡	1.05	1.88†	.01	1.49	4.32	<.001
Average	0.95	1.84†	<.001	0.80	2.77	<.001

Abbreviations: 23PSV, 23-valent pneumococcal polysaccharide vaccine; HIV, human immunodeficiency virus; PCV7, heptavalent pneumococcal conjugate vaccine.

* Comparison of geometric mean concentrations of IgG antibody before and after 23PSV vaccination by *t* test.

† $P < .05$ comparison between patients and controls by *t* test.

‡ Serotypes of pneumococcal capsular antigens included in both 23PSV and PCV7.

.001). The HIV-infected subjects produced lower post-23PSV titers than did the control subjects in 6 of the 12 serotypes tested (serotypes 1, 7F, 8, 9V, 18, and 23F in the younger group, and serotypes 1, 7F, 8, 9V, 14, and 23F in the older group; Table 2).

Clinical Protection Before and After 23PSV Vaccination

Before 23PSV vaccination, no significant difference was observed between the HIV-infected and control subjects in the levels of clinical protection against *S pneumoniae*. HIV-infected subjects had an average of 20.9% protection against invasive disease vs 17.5% in controls (Table 3). After 23PSV vaccination, both HIV-infected and control children developed higher clinical protection against invasive pneumococcal disease. HIV-infected children had significantly lower clinical protection after 23PSV vaccination in the younger group, however, no difference in clinical protection in the

older group when compared with the control group ($P = .007$ and .07, respectively).

The additional clinical protection gain after 23PSV vaccination was higher in control subjects when compared with the HIV-infected subjects (29.3% vs 14.4%, $P < .001$; Table 4). In HIV-infected subjects, children with a CD4⁺ cell count of 25% or higher at the time of vaccination developed more additional protective efficacy than did children with a CD4⁺ cell count of less than 25% (18.3% vs 0.5%; $P = .03$). Children with HIV infection with a CD4⁺ cell count of 25% or higher and a viral load of less than 50 copies/mL had the highest additional clinical protection gain after 23PSV vaccination (25.1%). There was no significant difference between CDC categories, viral load, age, or race at the time of vaccination in additional protective efficacy gain after 23PSV vaccination in HIV-infected subjects.

Table 3. Clinical Protection against Invasive *Streptococcus pneumoniae* of HIV-Infected Children and Control Children before and after 23PSV Vaccination*

Subject	Clinical protection, mean $\pm$ SD, %		P value†
	Pre-23PSV	Post-23PSV	
Total			
HIV	20.9 $\pm$ 22.9	35.2 $\pm$ 25.9	<.001
Controls	17.5 $\pm$ 15.0	46.8 $\pm$ 19.6‡	<.001
Younger children			
HIV	14.0 $\pm$ 18.5	28.4 $\pm$ 23.2	.003
Controls	16.2 $\pm$ 15.3	44.7 $\pm$ 19.7‡	<.001
Older children			
HIV	25.2 $\pm$ 24.8	39.6 $\pm$ 26.9	.01
Controls	23.0 $\pm$ 12.8	55.4 $\pm$ 17.4	<.001

Abbreviations: 23PSV, 23-valent pneumococcal polysaccharide vaccine; HIV, human immunodeficiency virus.

* Clinical protection represents the percentage of protection against invasive *S pneumoniae*, calculated using specific IgG level and incidence of invasive *S pneumoniae* isolated in the United States.

† Comparison before and after 23PSV vaccination by Wilcoxon signed rank test.

‡ $P < .05$ comparison among patients and controls by Mann-Whitney *U* test.

DISCUSSION

Previous studies demonstrate that HAART leads to immunologic reconstitution and improvement of host immunologic responses to various protein vaccinations.^{15,16} This study is the first to analyze the immunogenicity of polysaccharide vaccine of HIV-infected children while receiving stable

HAART. The characteristics of children in this study represent current HIV-infected children in developed countries in that they acquired their infection prenatally and had been given HAART. Children in this study had a previous history of severe immunodeficiency, with approximately 80% having a history of having CD4⁺ cell counts of less than 25%. However, at the time of vaccination, most children had relatively low viral loads and high CD4⁺ cell counts; 36.6% had undetectable viral RNA and 78% of the children had CD4⁺ cell counts of 25% or higher. One dose of 23PSV given to these children induced significant immunogenicity of most serotypes tested. This supports the belief that HAART led to improved immunological response to vaccines, including T-cell-independent polysaccharide vaccine. It also supports the current recommendation to give 23PSV vaccination to HIV-infected children receiving HAART.

Low baseline levels of specific IgG in HIV-infected children before 23PSV vaccination were consistent with the findings in other studies.^{5,17} Previous studies showed poor immunologic response and/or poor clinical benefit from 23PSV in HIV-infected patients,^{9,18} most of whom had not received HAART. King et al¹⁷ showed that HIV-infected children developed significant immunological responses to 23PSV in only 2 of 5 serotypes tested; in contrast, our study found significant responses to most serotypes. One major difference between the 2 studies was that the HIV-infected subjects in our study were receiving stable HAART before vaccination.

Another important finding of this study is that HIV-infected children with CD4⁺ cell counts greater than 25% at the time of vaccination developed better additional clinical pro-

Table 4. Additional Clinical Protection Against Invasive *Streptococcus pneumoniae* after 23PSV Vaccination in HIV-Infected Children and Control Children*

	Additional clinical protection, mean $\pm$ SD, %		P value
	Patients	Controls	
Total	14.4 $\pm$ 21.6	29.3 $\pm$ 20.4	<.001†
Younger children	14.3 $\pm$ 17.8	28.5 $\pm$ 21.0	.01†
Older children	14.4 $\pm$ 24.0	32.4 $\pm$ 17.7	.01†
HIV-infected children based on CD4 ⁺ T-cell count and viral load			
CD4 ⁺ T-cell count			
<25% (n = 9)	0.5 $\pm$ 19.7		.03‡
≥25% (n = 32)	18.3 $\pm$ 20.7		
Viral load, copies/mL			
<50 (n = 15)	16.9 $\pm$ 30.0		.57‡
≥50 (n = 26)	12.9 $\pm$ 15.4		
CD4 ⁺ T-cell count and viral load status			
CD4 ⁺ cell count <25% or viral load ≥50 copies/mL (n = 29)	9.9 $\pm$ 17.3		.04‡
CD4 ⁺ cell count ≥25% and viral load <50 copies/mL (n = 12)	25.1 $\pm$ 27.4		

Abbreviations: 23PSV, 23-valent pneumococcal polysaccharide vaccine; HIV, human immunodeficiency virus.

* Additional protection represents percent increase in clinical protection after 23PSV vaccination of each person; clinical protection represents percentage of protection against invasive *S pneumoniae*, calculated using specific IgG level and prevalence of invasive *S pneumoniae* isolated in the United States.

† Comparison among patients and controls by *t* test.

‡ Comparison among HIV-infected children by *t* test.

tection gain (18.3%) from 23PSV compared with no gain (0.5%) in children with CD4⁺ cell counts less than 25%. Moreover, children with both viral loads of less than 50 copies/mL and CD4⁺ cell counts of more than 25% had the highest benefit from the vaccine (25.1%), and the benefit resembled the control children (29.3%). This finding is consistent with studies performed in HIV-infected adults, which showed lower antibodies against *S pneumoniae* after vaccination when CD4⁺ cell counts were lower than 200 cells/mm³¹⁹ or showed a decreased incidence of invasive pneumococcal disease after vaccination when CD4⁺ cell counts were greater than 500 cells/mm³.²⁰ In addition, the average 14% clinical protection gain noted in HIV-infected children given the vaccine is a conservative number; the results should be higher if all 23 serotypes constituted in the 23PSV were analyzed and/or if a lower cutoff IgG level for immunologic protection was used.

Antibody responses are considered to be the principal mechanism of defense against invasive pneumococcal disease and have been widely used as an evaluation tool to study the efficacy of various pneumococcal vaccines.²¹ To apply the immunogenicity to the clinical efficacy, we later conferred the specific IgG antibody of each pneumococcal serotype to seropositivity and clinical protection based on specific IgG levels and the frequency of each serotype isolated. Although the specific IgG levels of adequate protection against pneumococcal invasive disease are not known, studies have suggested that systemic pneumococcal infection rarely occurs in persons who have IgG antibody titers greater than 1.5 to 1.8 µg/mL.^{22,23} In children, antibody titers of 1.25 µg/mL or higher were correlated with decreased nasopharyngeal colonization with specific pneumococcal serotype.²³ We conservatively used higher serotype specific IgG levels of 1.8 µg/mL as a cutoff value for a reliable immunologic protection. There are more than 90 pneumococcal serotypes with different immunogenicity and frequency for causing invasive diseases.²⁴ The 12 serotypes in this study represent most of the common serotypes isolated from invasive pneumococcal disease in US children older than 2 years and are responsible for 70% of such infection. The prevalence of serotype distribution of invasive pneumococcal diseases, obtained from a large population study and used in this study, was consistent with the prevalence of data from other studies.^{25,26} This prevalence should closely represent the prevalence in the HIV-infected population for the following reasons: (1) previous studies have not shown any difference in serotype distribution between HIV-infected and non-HIV-infected children,^{27,28} and (2) most invasive pneumococcal infections occur in HIV-infected persons, especially in areas where the HIV infection rate is high,^{28,29} as in our study population.

When cost and benefits are considered, the low cost and minimal adverse effects of 23PSV and the potential benefit of preventing invasive pneumococcal diseases strongly support the current recommendation. It may be prudent to give 23PSV to HIV-infected children when CD4 cell counts are

high or to revaccinate when they have increased CD4 cell counts with HAART.

ACKNOWLEDGMENTS

We thank Barbara Hyre for manuscript preparation and Tazim Verjee for editorial assistance.

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