MAJOR ARTICLE

Administration of Live Varicella Vaccine to HIV-Infected Children with Current or Past Significant Depression of CD4$^+$ T Cells

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Background. Varicella can be a severe illness in human immunodeficiency virus (HIV)–infected children. The licensed, live attenuated varicella vaccine is safe and immunogenic in HIV-infected children with minimal symptoms and good preservation of CD4$^+$ T cells (Centers for Disease Control and Prevention immunologic category 1).

Methods. To study the safety and immunogenicity of this vaccine in varicella-zoster virus (VZV)–naive, HIV-infected children with moderate symptoms and/or more pronounced past or current decreases in CD4$^+$ T cell counts, such children (age, 1–8 years) received 2 doses of vaccine 3 months apart. The children were observed in a structured fashion for adverse events. Blood was tested for VZV antibody and VZV-specific cell-mediated immunity (CMI) at baseline, 8 weeks after each dose, and annually for 3 years. Subjects who had no evidence of immunity 1 year after vaccination received a third dose and were retested.

Results. The vaccine was well tolerated; there were no vaccine-related, serious adverse events. Regardless of immunologic category, at least 79% of HIV-infected vaccine recipients developed VZV-specific antibody and/or CMI 2 months after 2 doses of vaccine, and 83% were responders 1 year after vaccination.

Conclusions. HIV-infected children with a CD4$^+$ T cell percentage of $\geqslant$15% and a CD4$^+$ T cell count of $\geqslant$200 cells/μL are likely to benefit from receiving varicella vaccine.

Varicella in healthy children can be associated with a variety of complications, most commonly bacterial superinfection [1–3]. Hospitalization was required after varicella developed in 1/600–1/1000 healthy children [4]. HIV-infected children are at increased risk of developing unusually severe and progressive varicella infection [5–7]. In addition, varicella can temporarily alter the care of an HIV-infected child, by complicating management in a clinic setting, interfering with adherence to therapy, or increasing the plasma HIV load by activating HIV-infected T cells.

In seeking to protect HIV-infected children from varicella, we previously undertook a pilot trial of the live attenuated varicella vaccine in children with asymptomatic or mildly symptomatic HIV infection [8]. The vaccine was well tolerated. Local or systemic reactions were similar in frequency to those observed in uninfected children. Moreover, 60% of HIV-infected vaccine recipients developed varicella-zoster virus (VZV) antibody, and 83% developed VZV-specific cell-mediated immunity (CMI) after 2 doses of vaccine.

We now extend these findings by reporting the persistence of vaccine-induced immunity at 1 year in children who were previously vaccinated and by administering varicella vaccine to 2 additional cohorts of HIV-infected children. These new vaccine recipients

Received 22 December 2005; accepted 3 March 2006; electronically published 14 June 2006.

Presented in part: Advisory Committee on Immunization Practices (Centers for Disease Control and Prevention), Atlanta, Georgia, 29 June 2005; International Herpesvirus Workshop VZV Satellite Symposium, Turku, Finland, 29 July 2005.

Potential conflicts of interest: M.J.L. has received research support and consultancy funds from Merck and shares with Merck a patent for a vaccine unrelated to the current study. A.A.G. has received consultancy funds from Merck and GlaxoSmithKline concerning use of varicella vaccines and has received honoraria from Merck for lectures.

Financial support: General Clinical Research Center Units, funded by the National Center for Research Resources (grant MO1RR00069 from the General Clinical Research Centers Program, National Center for Research Resources, National Institute of Allergy and Infectious Diseases [NIAID]); Pediatric AIDS Clinical Trials Group of the NIAID; Pediatric/Perinatal HIV Clinical Trials Network of the National Institute of Child Health and Human Development.

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The Journal of Infectious Diseases 2006; 194:247–55

0022-1899/2006/19402-0016$15.00

included either children with moderate symptoms (Centers for Disease Control and Prevention [CDC] clinical category B) and/or moderate immune suppression (CDC immunologic category 2) [9] or children who previously had advanced HIV infection (CDC clinical category C and/or immunologic category 3) but who had become asymptomatic and who had improved to CDC immunologic category 1 while receiving highly active antiretroviral therapy (HAART).

PATIENTS AND METHODS

Patient population. Vaccine recipients were 1–8 years of age, attended study sites of the Pediatric AIDS Clinical Trials Group (PACTG), had no history of varicella, and were seronegative for VZV antibody. Vaccine recipients were stratified into 3 groups. One group (group I) was in CDC clinical category 1 and immunologic category 1 (i.e., the least affected group of HIV-infected children) at the time of vaccination. The 3-month postvaccination data for this group of children have been reported elsewhere [8]. The subsequent, annual, postvaccination immune-response measurements for group I are reported here and are compared with measurements for the 2 new groups mentioned below. A prospectively chosen comparator group (not previously reported) consisting of HIV-infected subjects matched for the same clinical and immunologic categories as those of group I but who had had natural varicella during the year before entry in the trial was used for the present analysis.

A second group (group II) was in clinical category A, B, or N and immunologic category 2 ($CD4^+$ T cell percentage [CD4%], 15%–24%; $CD4^+$ T cell count for children 1–5 years of age, 500–999 cells/μL; $CD4^+$ T cell count for children $\geqslant$6 years of age, 200–499 cells/μL). A third group (group III) had been in CDC clinical category C and/or immunologic category 3, but, for at least 3 months prior to vaccination, had achieved clinical category A or N and the equivalent of immunologic category 1 (CD4%, $\geqslant$25%; $CD4^+$ T cell count for children 1–5 years of age, $\geqslant$1000 cells/μL; $CD4^+$ T cell count for children $\geqslant$6 years of age, $\geqslant$500 cells/μL).

Vaccine. Oka/Merck live varicella vaccine contained $\geqslant$1350 pfu of virus/0.5 mL at expiry. After written, informed consent was obtained from parents or guardians of the children (or written assent was obtained from children $\geqslant$7 years of age), subjects received vaccine subcutaneously at the beginning of the trial and 12 weeks later, which was the schedule previously used for HIV-infected children [8]. The vaccine was stored, handled, and administered according to information in the package insert.

Immunologic testing. Anti-VZV antibody was detected using the fluorescent antibody membrane assay (FAMA) [10]. VZV-specific CMI was measured using 2 methods. The first method measured the peripheral blood mononuclear cell (PBMC) response to VZV antigen, as assessed by a lymphocyte proliferation assay (LPA), as described elsewhere [11]. The stimulation index (SI) was defined as the counts per minute of radioactivity incorporated in the presence of VZV antigen divided by the counts per minute of radioactivity incorporated in the presence of control antigen. The second method involved enumeration of VZV-specific $CD4^+$ T memory cells by a responder cell frequency (RCF) assay by adding a limiting dilution step to the LPA [12]. The RCF assay used 24 replicate cultures of 6 serial 2-fold dilutions of PBMCs of 3125–100,000 cells/well. These cells were stimulated with VZV or mock-infected control antigen for 8 days, pulsed with [^{3}H]-thymidine for 6 h, and then harvested. The cells incorporated radioactivity measured in a scintillation counter. The RCF was calculated as described by Henry et al. [13]. Responder wells were defined as wells in which the counts per minute exceeded the mean counts per minute (+ 3 SD) of the control cultures at the same cell concentration. The percentage of nonresponder wells was plotted on a log scale against the number of cells per well plotted on a linear scale, and the RCF was interpolated at the 37% nonresponder-well frequency.

Plasma HIV RNA load. The HIV RNA load was quantified using the Amplicor HIV Monitor Test kit (Roche Diagnostics Systems), according to the manufacturer's instructions. The lower limit of quantitation was 400 HIV RNA copies/mL of plasma. The assays were performed in local laboratories certified by the PACTG.

Trial design (protocol ACTG 265 of the PACTG). No subjects could receive antiviral agents other than antiretroviral therapy. They could not receive immunobiologic agents or other vaccines for a prescribed period before or after vaccination, could not be receiving corticosteroid therapy, and had no recent exposure to VZV. Successfully screened subjects received 2 doses of varicella vaccine separated by 12 weeks. Weekly phone calls to the subjects and their parents/guardians were made for the first 3 weeks after each dose was received, to ascertain adverse reactions. Vaccine recipients maintained a diary card for 42 days, to record local and systemic signs, symptoms, and temperature. All lesions suggestive of varicella and other rashes occurring within 42 days after vaccination were examined in the clinic. Vaccine recipients had hematologic and chemical laboratory assessments performed on a regular basis. Immunologic testing was undertaken before vaccination; 8 weeks after each dose of vaccine was received; and 1, 2, and 3 years after vaccination. The naturally infected comparator subjects had immune testing performed at enrollment (1 year after natural varicella) and annually for 2 more years. The $CD4^+$ T cell count and the CD4% were determined at baseline; at 4, 8, and 12 weeks after the first dose of vaccine; and at 4, 8, 16, 28, and 40 weeks after the second dose. The plasma HIV RNA load was determined at baseline, at 4 and 12 weeks after the first dose of vaccine, and at 4 and 16 weeks after the second dose.

Table 1. Baseline demographic and clinical characteristics of HIV-infected children who received varicella vaccine or who had previous natural varicella.

Characteristic	Group with natural infection[a] (n = 15)	Group I (n = 43)	Group II (n = 37)	Group III (n = 17)	P
Sex					.54[b]
Male	3 (20)	16 (37)	16 (43)	9 (53)	
Female	12 (80)	27 (63)	21 (57)	8 (47)	
Race/ethnicity					.74[b]
White, non-Hispanic	2 (13)	14 (33)	7 (19)	3 (18)	
Black, non-Hispanic	10 (67)	20 (47)	22 (59)	9 (53)	
Hispanic	3 (20)	7 (16)	7 (19)	5 (29)	
Other[c]	0 (0)	2 (4)	1 (3)	0 (0)	
CDC clinical category					NA
N	4 (27)	16 (37)	6 (16)	11 (65)	
A	10 (67)	27 (63)	8 (22)	6 (35)	
B	1 (7)	0 (0)	23 (62)	0 (0)	
C	0 (0)	0 (0)	0 (0)	0 (0)	
Age, median (95% CI), years	5.2 (4.6–6.9)	4.0 (3.2–5.2)	5.0 (4.2–5.8)	6.2 (3.3–6.7)	.10[d]
$CD4^+$ T cell count, median (95% CI), cells/μL	1072 (914–1632)	1264 (1151–1487)	1022 (875–1181)	1387 (1003–2132)	.02[d]
CD4%, median (95% CI)	38 (28–41)	36 (32–39)	31 (29–35)	38 (34–48)	.02[d]
HIV RNA load,[e] median (95% CI), $\log_{10}$ copies/mL	NA	3.9 (3.3–4.4)	3.2 (2.6–4.1)	3.0 (2.6–3.5)	.02[d]

NOTE. CD4%, $CD4^+$ T cell percentage; CDC, Centers for Disease Control and Prevention; CI, confidence interval; NA, not applicable.

[a] The natural infection group had the same inclusion criteria as did group I, except that the naturally infected subjects had varicella during the year before study entry and had never received varicella vaccine.

[b] Comparison of groups I, II, and III by Fisher's exact test.

[c] Subjects in group I included 1 Asian, Pacific Islander, and 1 Native American; subjects in group II included 1 Asian, Pacific Islander.

[d] Comparison of groups I, II, and III by Kruskal-Wallis test

[e] RNA values at baseline were not available for the natural infection group; these values were available for 10 subjects in group I, 6 subjects in group II, and 3 subjects in group III.

At year 1 after vaccination, vaccine recipients who did not have detectable responses in both the antibody and CMI assays received an additional subcutaneous dose of the vaccine. These subjects were assessed for vaccine safety and immune response in the same manner that they were assessed after receipt of the first 2 doses of varicella vaccine.

Statistics. The Wilcoxon signed-rank test was used to test for changes in the $CD4^+$ T cell count, CD4%, and HIV RNA load. Logistic regression analysis was used to explore the association between immunologic responses (as determined by FAMA, LPA, and RCF) to varicella vaccination and independent variables, such as HIV RNA load, $CD4^+$ T cell count, and CD4%. An exact McNemar test with paired samples was used to test for changes from baseline with regard to FAMA, LPA, and RCF responses at weeks 8, 20, and 52, as well as changes in these responses from week 52 to week 64 for those subjects who received a third (booster) vaccination. The κ coefficient was used to test for agreement between FAMA, LPA, and RCF responses. In all cases, the significance level was $\alpha = 0.05$.

RESULTS

Demographic and clinical characteristics. The characteristics of the natural infection group and the 3 vaccine groups are shown in table 1. There were no significant differences in sex, race/ethnicity, or age at entry in the trial. Group II had more subjects in CDC clinical category B, as per the trial design. The median $CD4^+$ T cell count and the median CD4% were lower for group II than for groups I and III, because of the entry criteria for these groups, whereas the HIV RNA load at entry in the trial was highest in group I. Data on the baseline viral load were not available for the natural infection group.

Varicella vaccine safety. Table 2 presents the local and systemic events reported within 42 days after the administration of each of 2 doses of varicella vaccine. The adverse event profile did not differ significantly among the 3 vaccine groups. Injection-site reactions occurred in 6%–21% of subjects in each group after the first dose; overall, one-quarter of these reactions were grade 3 reactions (defined as 25–50 mm of induration/erythema or crying with touch); no subject refused the second dose because of a local reaction. Local reactions were half as common after the second dose, and only 1 such reaction was grade 3. The development of local reactions after the second dose was not more common in subjects who failed to develop an immune response after the first dose. Systemic adverse events (regardless of attribution to the vaccine) were reported in 12%–28% of subjects after the first dose; ~40% of these events were

Table 2. Local and systemic reactions noted 42 days after administration of varicella vaccine to HIV-infected children.

Group, reaction	Children with events after vaccination 1,[a] no. (%)		Children with events after vaccination 2,[a] no. (%)	
	Any event(s)	Grade 3 events	Any event(s)	Grade 3 events
I	(*n* = 42)	(*n* = 42)	(*n* = 42)	(*n* = 42)
Local	9 (21)	3 (7)	4 (10)	0 (0)
Systemic	12 (28)	2 (5)	7 (17)	0 (0)
Fever	6 (14)	2 (5)	2 (5)	0 (0)
Otitis/sinusitis	4 (9)	0 (0)	2 (5)	0 (0)
Rash	1 (2)	0 (0)	0 (0)	0 (0)
Viral syndrome	5 (12)	0 (0)	3 (7)	0 (0)
Other[b]	1 (2)	0 (0)	2 (5)	0 (0)
II	(*n* = 37)	(*n* = 37)	(*n* = 34)	(*n* = 34)
Local	3 (8)	1 (3)	1 (3)	0 (0)
Systemic	9 (24)	2 (5)	10 (29)	2 (6)
Fever	3 (8)	2 (5)	2 (6)	2 (6)
Otitis/sinusitis	2 (5)	0 (0)	3 (9)	0 (0)
Rash	1 (3)	0 (0)	1 (3)	0 (0)
Viral syndrome	2 (5)	0 (0)	3 (9)	0 (0)
Other[c]	4 (11)	0 (0)	4 (12)	1 (3)
III	(*n* = 17)	(*n* = 17)	(*n* = 17)	(*n* = 17)
Local	1 (6)	0 (0)	2 (12)	1 (6)
Systemic	2 (12)	0 (0)	5 (29)	1 (6)
Fever	0 (0)	0 (0)	2 (12)	0 (0)
Otitis/sinusitis	1 (6)	0 (0)	1 (6)	0 (0)
Rash	0 (0)	0 (0)	0 (0)	0 (0)
Viral syndrome	1 (6)	0 (0)	1 (6)	0 (0)
Other[d]	0 (0)	0 (0)	4 (24)	1 (6)

[a] Some children had >1 event.

[b] Other events after vaccination 1 included grade 1 sore throat (*n* = 1) and grade 2 sore throat (*n* = 1). Other events after vaccination 2 included grade 2 allergic reaction (*n* = 1).

[c] Other events after vaccination 1 included grade 1 headache (*n* = 1), grade 1 nausea (*n* = 1), grade 1 vomiting (*n* = 1), grade 2 neutropenia (*n* = 1), and grade 2 increased serum amylase level (*n* = 1). Other events after vaccination 2 included pneumonia unrelated to vaccine (*n* = 1), grade 2 otitis (*n* = 1), grade 4 seizure (*n* = 1), grade 2 thrombocytopenia (*n* = 1), and grade 2 neutropenia (*n* = 1).

[d] Other events after vaccination 1 included grade 1 otitis (*n* = 1). Other events after vaccination 2 included pneumonia unrelated to vaccine (*n* = 3), diarrhea (*n* = 1), and grade 4 neutropenia (*n* = 1).

fever, and the remainder were mostly otitis media and upper-respiratory-tract symptoms characteristic of children of this age. Fever was grade 3 (temperature, 39.4°C–40.5°C) in <5% of all vaccine recipients after the first dose and in <3% after the second dose. Eighteen subjects (10 in group I, 5 in group II, and 3 in group III) received a booster dose of varicella vaccine 1 year after the initial 2-dose series. In group I, after the third dose, a single injection-site reaction and 2 systemic adverse events (1 viral syndrome and 1 sore throat) occurred.

Four subjects were reported to have pneumonia at days 21, 27, 30, and 37 after receipt of the second dose of vaccine. All were designated by the clinical provider at the study site as having intercurrent seasonal viral infection (all cases occurred in October through January) and as having cases unrelated to vaccine. All subjects were sent home without antiviral therapy and were well at routine follow-up. Nineteen days after receipt of the second vaccine, a seizure occurred in a child with a temperature of 41.3°C. After an emergency department evaluation that included cerebrospinal fluid examination and brain computed tomography, this child was sent home while receiving nonsteroidal anti-inflammatory drugs. Ten days after the seizure, otitis media was detected and was treated with antibiotics. The seizure was considered to be possibly a vaccine-related febrile seizure.

There were no clinically significant changes in $CD4^+$ T cell counts or CD4% values in any group (I, II, or III) after any scheduled dose, when testing was done 1 month after vaccination (data not shown). One subject had a 50% decrease in the $CD4^+$

Table 3. Antibody response to administration of varicella vaccine to HIV-infected children.

Group	Positive FAMA result,[a] by study week						
	0	8	20	52	64[b]	104	156
I	0/42 (0)	20/37 (54)	23/39 (59)	16/37 (43)	5/12 (42)	12/33 (36)	14/27 (52)
II	0/35 (0)	22/35 (63)	23/32 (72)	18/31 (58)	1/3 (33)	12/24 (50)	6/21 (29)
III	0/17 (0)	10/16 (63)	12/17 (71)	11/17 (65)	1/3 (33)	7/15 (47)	5/13 (38)
Natural infection	11/11 (100)	3/3 (100)	ND	8/11[c] (73)	ND	7/13[d] (54)	3/10 (30)

NOTE. Data are no. of children with a positive fluorescent antibody membrane assay (FAMA) result/total no. of children evaluated (% of children with a positive FAMA result). ND, not done.

[a] A positive result was denoted by an antibody titer of ⩾1:2.

[b] Data represent the response in children who had undetectable FAMA and cell-mediated immunity responses at week 52 and who received a third dose of vaccine at week 56.

[c] Difference from other groups, $P = .26$.

[d] Difference from group I, $P = .66$.

T cell count 29 days after receipt of a booster (third) dose of the vaccine. However, this child's prevaccination $CD4^+$ T cell count was considered to be spuriously high, on the basis of multiple previous and recent determinations. No subject in these groups had a change in their CDC clinical category after a dose of vaccine. A vaccine-related rash was reported 14 days after the first vaccination and at 3 and 22 days after the second vaccination.

Immunogenicity. Depending on the group, 59%–72% of vaccine recipients developed an antibody response after the second dose of vaccine, and 43%–65% had detectable antibody at 1 year after vaccination (table 3). HIV-infected children who had mild symptoms and/or were in CDC immunologic category 2 (group II) were no less likely to have an antibody response to the varicella vaccine than were subjects who were less affected by HIV infection (group I). Furthermore, children who returned to CDC immunologic category 1 after being in immunologic category 3 (group III) were as responsive, but not more so, than the other groups. The likelihood of developing a detectable antibody response was not significantly increased in any group by a second dose of vaccine (week 20 vs. week 8). The proportion of vaccine recipients who had detectable antibody 1 year after vaccination was similar to the proportion of antibody-positive control subjects who had had natural varicella 1 year previously. Overall, <50% of vaccine recipients (7 of 18 vaccine recipients) who had no evidence of VZV-specific immunity at 1 year developed detectable antibody after a third dose of vaccine. At 2 and 3 years after vaccination, ⩽50% of vaccine recipients had detectable antibody, similar to the persistence of antibody in the naturally infected subjects.

Measurement of VZV-specific CMI after varicella vaccination was achieved using 2 assay methods. LPA indicated that two-thirds of each group developed CMI after the first dose of vaccine was administered (table 4). This interpretation was complicated by the fact that many subjects had a positive result

Table 4. Response to administration of varicella vaccine to HIV-infected children, as determined by lymphocyte proliferation assay (LPA).

Group, cohort	Positive LPA result,[a] by study week							Mean SI,[b] by study week					
	0	8	20	52	64	104	156	8	20	52	64	104	156
I													
All	13/42	23/33	24/33	28/37	7/11	22/32	15/26	9.5	10.2	11.0	6.2	8.9	7.4
BaseNeg	…	11/20	14/20	19/27	4/8	15/22	11/20	6.6	8.9	9.6	4.9	10.9	6.6
II													
All	6/35	21/32	19/25	23/27	2/2	12/21	7/17	8.6	21.3	27.2	4.7	9.7	5.8
BaseNeg	…	16/26	16/20	18/23	2/2	11/19	6/14	7.3	24.8	26.0	4.7	11.5	6.2
III													
All	1/17	12/15	11/13	12/13	0/0	11/13	4/12	18.8	26.4	20.6	39.0	21.4	3.5
BaseNeg	…	12/14	10/12	12/13	…	11/12	4/12	22.5	22.0	20.6	39.0	27.0	3.5
Natural infection	…	…	…	8/12	…	6/11	7/10	…	…	6.1	3.0	…	10.8

NOTE. LPA was performed at ~80% of the time points specified; 40% of children had both LPA and a responder cell frequency assay performed at the same time. BaseNeg, subjects for whom the LPA result at baseline (week 0) was negative; SI, stimulation index.

[a] Defined as an SI of ⩾3.0. Data are no. of children with a positive LPA result/total no. of children evaluated.

[b] The SI was defined as the counts per minute of radioactivity incorporated in the presence of varicella-zoster virus antigen, divided by the counts per minute of radioactivity incorporated in the presence of control antigen. The no. of children with data used in the calculation of the mean SI during each study week is the same as the total no. of children who were evaluated by LPA during the corresponding study week.

Table 5. Response to administration of varicella vaccine to HIV-infected children, as determined by responder cell frequency (RCF) assay.

	Positive RCF assay result,[b] by study week						
Group[a]	0	8	20	52	64[c]	104	156
II	1/24 (4)	11/17 (65)	14/20 (70)	14/16 (88)	0/3 (0)	12/14 (86)	5/12 (42)
III	1/16 (6)	7/12 (58)	9/14 (64)	12/15 (80)	3/4 (75)	8/13 (62)	7/10 (70)

NOTE. Data are no. of children with a positive result/total no. of children evaluated (% of children with a positive result). An RCF assay was not performed for 10% of the time points specified; an RCF assay was performed with a lymphocyte proliferation assay (LPA) for 40% of the time points.

[a] An RCF assay was not performed routinely for group I [8].

[b] A positive result was defined as ⩾1 memory cell/10^5 peripheral blood mononuclear cells.

[c] Data denote a response in children who had both undetectable fluorescent antibody membrane assay and cell-mediated immunity responses at week 52 and who received a third dose of vaccine at week 56.

at baseline. This problem was previously observed by us [8] and was thought to be the result of nonspecific PBMC activation associated with immune stimulation engendered by HIV replication. This explanation for the presumed false-positive results at baseline is consistent with the finding that all of the baseline values were negative for subjects in group III, who required stable HAART (and, thus, less nonspecific activation) as an entry criterion. Group III had the lowest median HIV RNA load and the highest median $CD4^+$ T cell count. When the subjects with a negative LPA result at baseline were analyzed separately (table 4), the likelihood of developing a positive CMI result remained 60%–65%. There were no significant differences between the groups with respect to either the proportion of subjects with a positive assay result or the median SI after the first dose of vaccine. The administration of a second dose of vaccine did not significantly increase the proportion of subjects with a positive LPA response in any group. The LPA response noted at 1 year (⩾70%) was similar in all vaccine recipients and was 67% in the naturally infected control subjects. A third dose of vaccine induced an LPA response in ~70% of vaccine recipients who had no detectable immune response 1 year after the initial vaccine series was administered.

The RCF assay was performed as a pilot assay restricted to 10 subjects in group I, so data from this assay are presented only for groups II and III. The RCF assay appeared to be more sensitive and specific than the LPA, with positive baseline values noted for <5% of subjects (table 5). Two-thirds of vaccine recipients in groups II and III had VZV-specific CMI detectable by RCF assay after 2 doses of vaccine, as did ~80% of them at 1 year after vaccination. There was reasonable agreement between the 2 CMI assays, as well as between the RCF and antibody assays. Formal tests of association, with use of Cohen's κ statistic, were performed using data from week 20, after all subjects had received 2 doses of vaccine (for LPA vs. the RCF assay, $\kappa = 0.61$ and $P = .04$; for FAMA vs. the RCF assay, $\kappa = 0.51$ and $P = .006$; for FAMA vs. LPA, $\kappa = 0.32$ and $P = .06$).

A composite analysis of all of the immune responses combined indicated that >83% of the subjects developed ⩾1 VZV-specific immune response after vaccination (table 6). In this analysis, 11 (61%) of 18 vaccine recipients who had no response at 1 year after vaccination did respond to a third dose of vaccine. Furthermore, two-thirds of vaccine recipients had some evidence of VZV-specific immunity 2 years after vaccination,

Table 6. HIV-infected children with any varicella-zoster virus (VZV)–specific immune response noted after administration of varicella vaccine.

	Any VZV-specific response,[a] by study week						
Group	0	8	20	52	64[b]	104	156
Vaccinated children							
Group I[c]	0/30 (0)	18/26 (69)	23/29 (79)	24/29 (83)	6/10 (60)	17/28 (61)	16/25 (64)
Group II	0/31 (0)	22/31 (71)	25/29 (86)	23/27 (85)	2/5 (40)	15/23 (65)	12/23 (52)
Group III	1/16 (0)	12/16 (75)	13/15 (87)	14/15 (93)	3/3 (100)	11/15 (73)	10/15 (67)
All	1/77 (0)	52/73 (72)	61/73 (84)	61/71 (86)	11/18 (61)	43/66 (65)	38/63 (60)
Naturally infected children	11/11 (100)	3/3 (100)	0/1 (0)	9/12[c] (75)	NA	10/13 (77)	8/11 (73)

NOTE. Data are the no. of children with any VZV-specific response detected/total no. of children evaluated (% of children with any VZV-specific response detected). NA, not applicable.

[a] Data for children who had positive immune responses at baseline and who were vaccinated were not included in this table.

[b] This cohort did not receive a booster dose at week 64 if any immune responses were noted at week 52.

[c] This cohort did not have responder cell frequency determined.

Table 7. Univariate logistic-regression analyses of fluorescent antibody membrane assay (FAMA), lymphocyte proliferation assay (LPA), and responder cell frequency (RCF) assay responses at study weeks 8, 20, and 52.

	FAMA antibody response[a]		LPA[b]		RCF assay[c] (⩾1.0)	
Time point, independent variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Week 8						
Baseline $\log_{10}$ HIV RNA copies/mL	0.300 (0.147–0.560)	.0004	0.250 (0.105–0.528)	.001	0.304 (0.079–0.930)	.05
Baseline CD4%	0.989 (0.944–1.035)	.64	1.029 (0.976–1.057)	.30	1.083 (0.986–1.213)	.12
Week 20						
Baseline $\log_{10}$ HIV RNA copies/mL	0.533 (0.294–0.931)	.03	0.659 (0.324–1.316)	.24	0.285 (0.096–0.729)	.01
Baseline CD4%	0.983 (0.934–1.033)	.49	1.032 (0.970–1.103)	.33	0.977 (0.893–1.067)	.61
Week 52						
Baseline $\log_{10}$ HIV RNA copies/mL	0.446 (0.249–0.823)	.01	0.669 (0.306–1.453)	.30	0.474 (0.131–1.661)	.24
Baseline CD4%	1.019 (0.974–1.068)	.42	0.991 (0.934–1.054)	.78	0.951 (0.851–1.055)	.34

NOTE. CD4%, $CD4^+$ T cell percentage; CI, confidence interval; OR, odds ratio.

[a] FAMA, ⩾2.

[b] Stimulation index, ⩾3.

[c] RCF, ⩾1/10^5 peripheral blood mononuclear cells.

which was similar to the proportion of responders who had prior natural infection.

Logistic-regression analysis demonstrated that most post–dose 1 and post–dose 2 immune responses were significantly correlated with the immediate prevaccination HIV RNA load (table 7). There was no association of these responses with $CD4^+$ T cell count or CD4% at the time of the first vaccination. Multivariate analysis indicated that the effect of the HIV RNA load was independent of $CD4^+$ T cell status (data not shown). In general, the likelihood of an antibody response at years 2 and 3 after vaccination was greatest when results of the preceding tests were positive (data not shown).

Outcome of exposure to varicella. The present study and its predecessor were not powered to determine vaccine efficacy. Information on outcomes after exposure to varicella was obtained according to a protocol-specified format provided to the clinic. There were 16 reported exposures to VZV (from a playmate [$n = 12$], in the hospital [$n = 1$], and in the household [$n = 3$]); only 1 subject was given varicella-zoster immune globulin. One child with <50 lesions was judged to have varicella after an unappreciated exposure. One child had a possible herpes zoster 1 year after vaccination.

DISCUSSION

The licensed, live attenuated VZV vaccine was previously demonstrated to be safe and well tolerated in HIV-infected children who are asymptomatic or have minimal symptoms and are in CDC immunologic category 1 [8]. We have now demonstrated that VZV vaccination is also well tolerated by HIV-infected children in CDC clinical category B and/or immunologic category 2 and in children in whom reconstitution of the CD4% resulted in a change from CDC immunologic category 3 to category 1. The type and frequency of adverse events that were not related to the injection site and that were reported over a 6-week postvaccination period in these HIV-infected children were typical of uninfected vaccine recipients of this age [14, 15]. There were no clinically significant differences in adverse events among the 3 vaccinated groups, even though they differed according to past or current $CD4^+$ T cell status. The serious adverse events that were recorded mirrored those previously reported in uninfected vaccine recipients, except for 1 febrile seizure that was questionably related to the vaccine. There were 4 episodes of "pneumonia" that occurred during the study, but none were considered to be related to the vaccine. Immunization with this live virus did not cause any clinically significant effect on HIV RNA load or $CD4^+$ T cell status. The second or third dose of varicella vaccine was administered without any evidence of sensitization. In fact, possible vaccine-related adverse events were less common after administration of subsequent doses, suggesting that specific immune responses induced by the first dose modulated replication of vaccine virus injected with subsequent doses, as has been observed in HIV-infected and -uninfected vaccine recipients [8, 16]. To date, observations of responses to varicella vaccine are in accordance with the safe use of another live attenuated vaccine, measles-mumps-rubella, in HIV-infected children [17].

VZV-specific antibody was induced in 60%–70% of vaccine recipients, which is similar to results reported for other groups of immunocompromised children [18]. The response rate was similar in the 3 vaccine groups, despite differences in past or current $CD4^+$ T cell status in these groups. This lack of an association between immune responsiveness and CDC immunologic staging is subject to the limitations of the narrow range of the CD4% at baseline among the study participants and the small number of subjects studied. In contrast, responses rates did correlate significantly with the HIV RNA load at the

time of vaccination, independent of the CD4%. This association with a live vaccine was observed in the first study of varicella vaccination of HIV-infected children [8], and a similar association was observed between HIV load and immune responses to hepatitis A and B virus vaccines [19–21]. The practical implication of these observations is that viral load, as well as $CD4^+$ T cell status, should be a consideration in deciding when to vaccinate HIV-infected children.

The comparison of immunologic response rates after 1 or 2 doses of vaccine did not demonstrate significant added value from the second dose, although this does not preclude an important role played by a second dose in the persistence of detectable antibody over an extended period. A small number of subjects failed to have a response to vaccination or lost VZV-specific immune responses by 1 year after vaccination. In our logistic-regression analysis, we were unsuccessful in defining characteristics that could distinguish between "responders" and "nonresponders" at 1 year after vaccination, although our study population was small. Administration of a third dose of vaccine restored detectable antibody in two-thirds of nonresponding subjects.

Antibody measurements in immunocompromised patients have previously been found to underestimate varicella vaccine responses and efficacy [8, 18, 22]. In the current study, the varicella vaccine induced a VZV-specific CMI response in >80% of vaccine recipients, as measured by $\geq$1 of the immune assays at 1 year after immunization; in most cases, several assays had positive results. Furthermore, the proportion of subjects with a positive antibody test result at 2–3 years after vaccination was similar to that of HIV-infected control subjects who had prior natural infection with varicella. The 2 CMI assays, RCF assay and LPA, were highly correlated, but the RCF assay emerged as superior to LPA because of specificity (baseline issues) and sensitivity, even though the blood specimens were delivered by overnight mail.

Although only 97 HIV-infected children received varicella vaccine, the detection of a VZV-specific immune response measured by at least 1 immune assay (CMI and/or antibody) in 85% of vaccine recipients is important, because prior receipt of varicella vaccine in HIV-uninfected children, as well as in other immunocompromised patients, suggests that the appearance of vaccine-induced immunity correlates with the prevention of acquisition or reactivation of VZV infection and that, when breakthrough disease occurs in responding vaccine recipients, the resulting illness is attenuated [22, 23]. Just as varicella vaccine was recommended for mildly affected HIV-infected children, it is now possible to extend these recommendations to additional HIV-infected children, as defined by the groups studied in the present trial. This would be easily accomplished by requiring a CD4% of $\geq$15% and a $CD4^+$ T cell count of $\geq$200 cells/μL to qualify for vaccination, which is the current requirement for administration of measles-mumps-rubella vaccine to HIV-infected children [17]. The need for 2 doses of vaccine was not proved in this trial, but it should be retained until this can be studied further. The efficacy of varicella vaccination in this setting is undefined and probably will remain so until large-scale efficacy trials can be undertaken in areas where varicella is endemic. The decrease in VZV-specific immune responses with time raises questions about the persistence of potential protection. However, a similar decrease occurred in our naturally infected control subjects, and naturally infected children do not experience second cases of varicella. The value of additional booster doses will be determined after prolonged observation of HIV-infected children who have been vaccinated.

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