MAJOR ARTICLE

Safety and Immunogenicity of an Adjuvanted Herpes Zoster Subunit Candidate Vaccine in HIV-Infected Adults: A Phase 1/2a Randomized, Placebo-Controlled Study

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Background. Human immunodeficiency virus (HIV)–infected individuals are at increased risk of herpes zoster (HZ), even in the antiretroviral therapy (ART) era. Because concerns exist about the use of live-attenuated vaccines in immunocompromised individuals, a subunit vaccine may be an appropriate alternative.

Methods. This phase 1/2, randomized, placebo-controlled study evaluated the immunogenicity and safety of an investigational HZ subunit vaccine (HZ/su). Three cohorts of HIV-infected adults aged ≥18 years were enrolled: 94 ART recipients with a $CD4^+$ T-cell count of ≥200 cells/mm^3, 14 ART recipients with a $CD4^+$ T-cell count of 50–199 cells/mm^3, and 15 ART-naive adults with a $CD4^+$ T-cell count of ≥500 cells/mm^3. Subjects received 3 doses of HZ/su (50 μg varicella-zoster virus glycoprotein E [gE] combined with $AS01_B$ adjuvant) or 3 doses of saline at months 0, 2, and 6.

Results. One month after dose 3, serum anti-gE antibody concentrations and frequencies of gE-specific $CD4^+$ T cells were higher following HZ/su vaccination than after receipt of saline ($P < .0001$). Median cell-mediated immune responses peaked after dose 2. Humoral and cell-mediated immune responses persisted until the end of the study (month 18). No vaccination-related serious adverse events were reported. No sustained impact on HIV load or $CD4^+$ T-cell count was noted following vaccinations.

Conclusions. HZ/su was immunogenic and had a clinically acceptable safety profile in HIV-infected adults.

Clinical Trials Registration. NCT01165203.

Keywords. herpes zoster; zoster vaccine; HIV infection; varicella-zoster virus; immunodeficiency; glycoprotein E.

Herpes zoster (HZ; commonly known as shingles) is an often debilitating disease resulting from the reactivation of latent varicella-zoster virus (VZV) infection [1]. The incidence of HZ in the general population is 2.0–3.6 cases per 1000 person-years, with higher incidence rates in adults ≥50 years of age and in immunocompromised people, including human immunodeficiency virus (HIV)–infected individuals [2–4]. Cell-mediated immunity (CMI) plays a major role in controlling VZV reactivation, and CMI in HIV-infected individuals can be substantially and persistently compromised [5–7].

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Before the introduction of highly active antiretroviral therapy (ART), HZ incidence rates were 10–20 times higher in HIV-infected adults than in the age-matched general population [2, 3, 8–11]. Since ART was introduced, HZ incidence rates have decreased to approximately 10 cases per 1000 person-years but remain 3–5 times higher than in the general population [2, 12, 13]. HZ may occur at any time during HIV infection [3, 10, 14], although a low $CD4^+$ T-cell count and an HIV RNA level of >400 copies/mL have been associated with higher risks of HZ [2, 8]. Furthermore, recurrent HZ cases are more frequent in HIV-infected individuals [2, 8, 10, 14]. Similar to the incidence of HZ itself, complication rates are also higher in HIV-infected subjects than in the age-matched general population (27%–28% vs 10%–13%) [2, 4, 8] and include cutaneous dissemination, chronic atypical skin lesions, or ocular and neurological complications [2, 8, 15, 16].

Because of the high incidence of HZ and its complications, vaccination offers the potential for substantial benefit in HIV-infected individuals. However, concerns exist about the use of the licensed HZ live-attenuated vaccine (Zostavax; Merck) for immunocompromised individuals, including some HIV-infected subpopulations, because of its potential to cause disease [1, 17]. A recombinant subunit vaccine may thus be an appropriate alternative for preventing HZ in this population [1, 18].

VZV glycoprotein E (gE) is a promising HZ vaccine antigen because it is a major target of anti-VZV cellular and humoral immune responses [5, 19–21]. Phase 1/2 and phase 2 randomized trials showed that a subunit HZ vaccine candidate (HZ/su) consisting of 50 μg gE and the liposome-based adjuvant system $AS01_B$ induced strong and durable cellular and humoral immune responses and had a clinically acceptable safety profile in healthy older adults [22–24]. In this population, 2 doses of HZ/su were strongly immunogenic. However, in HIV-infected individuals, it is not known whether 2 doses would generate a similarly robust immune response or whether a third dose would substantially enhance it. Thus, in the current study, HIV-infected adults received 3 doses of HZ/su, and immunogenicity was evaluated after 2 and 3 doses. Furthermore, safety and reactogenicity of HZ/su were evaluated in this immunocompromised population.

METHODS

Study Design

This phase 1/2a, randomized, observer-masked, placebo-controlled, multicenter study evaluated the safety and immunogenicity of the HZ/su vaccine candidate (GlaxoSmithKline Vaccines) in comparison to saline when administered as a 3-dose schedule to HIV-infected adults (clinical trials registration: NCT01165203). The study was conducted at 15 centers in Germany, the United States, and the United Kingdom between 30 September 2010 and 14 May 2013.

The study was performed in accordance with the Declaration of Helsinki and good clinical practice guidelines. The study protocol and the informed consent form were approved by a national, regional, or investigational independent ethics committee or institutional review board. All subjects gave written informed consent before enrollment.

The study included 3 cohorts of HIV-infected subjects: ART recipients with a high $CD4^+$ T-cell count (≥200 cells/mm^3), ART recipients with a low $CD4^+$ T-cell count (50–199 cells/mm^3), and ART-naive adults with a high $CD4^+$ T-cell count (≥500 cells/mm^3). The target sample size was 45 subjects for each cohort (Supplementary Materials). However, if enrollment rates were slow in the ART/low $CD4^+$ T-cell count and ART-naive cohorts, the study protocol allowed the sizes of these cohorts to be decreased and the size of the ART/high $CD4^+$ T-cell count cohort to be correspondingly increased.

Subjects

HIV-infected adults ≥18 years of age who received a diagnosis of HIV infection at least 1 year before enrollment were included in the study. For inclusion in the 2 ART-treated cohorts, subjects were required to have been receiving a stable ART regimen for at least 1 year (defined no change because of virological or immunological failure) and to have a $CD4^+$ T-cell count of ≥50 cells/mm^3 and an HIV RNA load of <40 copies/mL at screening. For inclusion in the ART-naive cohort, subjects could not have received ART or be expected to start ART within the next 7 months, and they were required to have a $CD4^+$ T-cell count of ≥500 cells/mm^3 and an HIV load of ≥1000 and ≤100 000 copies/mL at screening. Women were to be of nonchildbearing potential or using a highly effective contraception with a negative pregnancy test result on the day of vaccination.

Subjects were excluded from the study if they had a varicella/HZ episode or received vaccination against varicella/HZ within the previous 12 months; an AIDS-defining condition at enrollment, according to the 2008 criteria of the Centers for Disease Control and Prevention [25]; an opportunistic infection (other than oral thrush) or AIDS-associated malignancy in the previous year; any immunocompromised condition resulting from disease other than HIV infection or immunosuppressive/cytotoxic therapy; ongoing treatment with HIV fusion inhibitors, CCR5 inhibitors, or interleukin 2/interleukin 7/interferon gamma; or abnormal biochemical and hematological laboratory values at screening. Subjects in the ART cohorts were also excluded if their antiretroviral drug regimen had been changed within 12 weeks before vaccination (full inclusion and exclusion criteria are available in the Supplementary Materials).

Vaccinations

Subjects in each of the 3 cohorts were randomly assigned at a ratio of 3:2 to receive either 3 doses of the adjuvanted recombinant vaccine candidate (HZ/su) or 3 doses of saline (placebo) at study months 0, 2, and 6. Vaccines were administered intramuscularly in the deltoid muscle of the nondominant

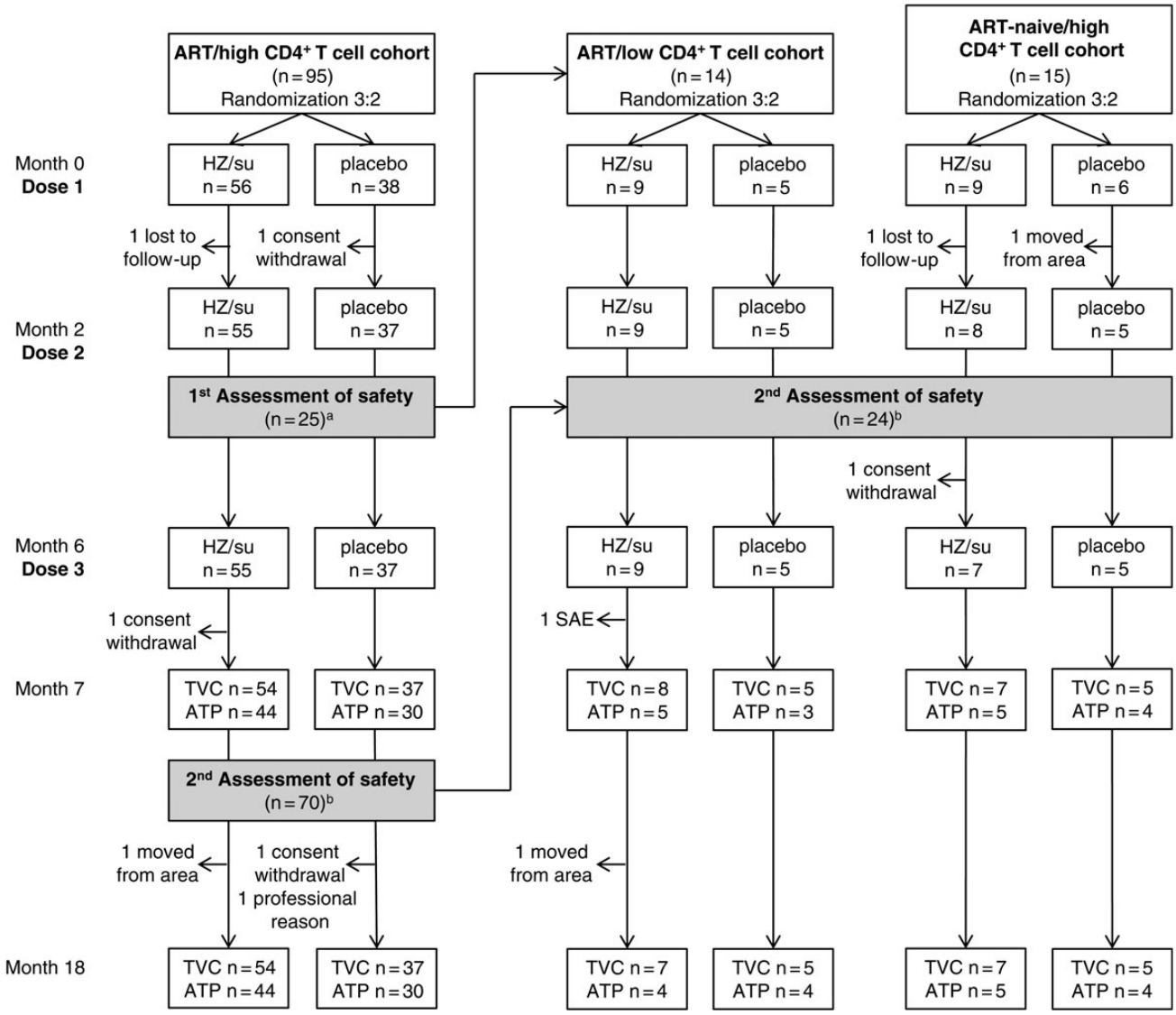

Figure 1. Subject disposition. Herpes zoster (HZ) subunit vaccine (HZ/su) was first administered to human immunodeficiency virus (HIV)–infected subjects receiving antiretroviral therapy (ART) with a $CD4^+$ T-cell count of ≥200 cells/mm^3. *A*, Once the safety of 2 doses of HZ/su had been evaluated in the first 25 subjects (24 subjects with 2 doses and 1 subject with 1 dose) in this cohort by a safety committee composed of GlaxoSmithKline physicians and statistician and 1 non–GlaxoSmithKline-affiliated HIV expert, enrollment was initiated for subjects receiving ART with a lower $CD4^+$ T-cell count (50–199 cells/mm^3) and ART-naive subjects ($CD4^+$ T-cell count, ≥500 cells/mm^3). *B*, A similar process was followed after administration of the third dose in the ART/high $CD4^+$ T-cell count cohort (in 70 subjects: 38 with 3 doses, 7 with 2 doses, and 25 with 1 dose) and after the second dose in the ART/low $CD4^+$ T-cell count and ART-naive cohorts (in 24 subjects: 10 with 2 doses and 14 with 1 dose). Once safety had been evaluated, vaccination with the third dose was started in these 2 cohorts. Abbreviations: ATP, according-to-protocol cohort; TVC, total vaccinated cohort.

arm. HZ/su contained 50 μg of lyophilized recombinant VZV gE antigen reconstituted with 0.5 mL of liposome-based $AS01_B$ adjuvant (50 μg of monophosphoryl lipid A and 50 μg of *Quillaja saponaria* Molina 21; Antigenics, Lexington, MA). Engineering, purification, and characterization of the recombinant gE vaccine antigen has been previously described [26].

Preparation and administration of vaccines was done by authorized medical personnel who did not participate in any clinical evaluation of the subjects. The subjects and the personnel responsible for the evaluation of any study end point were unaware of whether vaccine or placebo had been administered.

Study enrollment was conducted in a stepwise approach (Figure 1). First, HZ/su was administered to subjects in the ART/high $CD4^+$ T-cell count cohort. Once the safety of 2 HZ/su doses had been evaluated by a safety committee composed of GlaxoSmithKline personnel and 1 non–GlaxoSmithKline-affiliated HIV expert for the first 25 subjects in this cohort, enrollment was initiated for subjects in the ART/low $CD4^+$ T-cell count and ART-naive/high $CD4^+$ T-cell count cohorts. Similarly,

the safety of the third dose in the ART/high $CD4^+$ T-cell count cohort and of the second dose in the ART/low $CD4^+$ T-cell count and ART-naive/high $CD4^+$ T-cell count cohorts was evaluated before third doses were administered to the ART/low $CD4^+$ T-cell count and ART-naive/high $CD4^+$ T-cell count cohorts.

Assessment of Immunogenicity

Blood samples were collected at months 0 (before vaccination), 1, 2, 3, 6, 7, and 18. The frequency of $CD4^+$ T cells expressing at least 2 activation markers (among interferon γ, interleukin 2, tumor necrosis factor α, and CD40 ligand) per 10^6 $CD4^+$ T cells, hereafter referred to as CD4(2+) T cells, was measured after in vitro stimulation with gE or VZV by intracellular cytokine staining followed by flow cytometry, as previously described [23]. A cell-mediated immune response to the vaccine was defined as a ≥2-fold increase over the prevaccination baseline in the frequency of CD4(2+) T cells after induction with gE or VZV.

Anti-gE antibody concentrations were measured by enzyme-linked immunosorbent assay (GlaxoSmithKline Vaccines). An anti-gE humoral immune response to the vaccine was defined as an anti-gE antibody concentration ≥4-fold the assay cutoff (18 mIU/mL) in initially seronegative subjects and as an antibody concentration ≥4-fold the prevaccination concentration in initially seropositive subjects.

Assessment of Safety and Reactogenicity

Solicited local reactions (pain, redness, and swelling at the injection site) and general reactions (fever, headache, fatigue, gastrointestinal symptoms, myalgia, and shivering) were reported by subjects on diary cards for 7 days after each dose. Intensity was scored on a scale of 0 (absent) to 3 (severe). Unsolicited adverse events (AEs) were reported by subjects on diary cards for 30 days after each dose. Serious AEs (SAEs), new onset of immune-mediated inflammatory diseases, worsening of HIV disease, and HZ cases were reported throughout the study. Worsening of HIV disease was defined as a prespecified change in HIV RNA level (for ART cohorts, defined as detectable HIV RNA 1 month after vaccination; for the ART-naive cohort, defined as a 0.5-log increase 1 month after vaccination, compared with the levels at screening or the previous vaccination visit) or in $CD4^+$ T-cell count (defined as a >30% decrease at months 1–7, compared with the count at screening or the previous vaccination visit), emergence of an AIDS-defining condition, or a change to ART because of immunological or virological failure, including ART initiation in the ART-naive/high $CD4^+$ T-cell count cohort. Hematological and biochemical analyses were performed in blood samples at screening and at months 1–7.

Statistical Analysis

For months 0–7, immunogenicity was analyzed in the according-to-protocol cohort for immunogenicity (defined as all subjects vaccinated according to the study procedures with immunogenicity data available); for month 18, immunogenicity was analyzed in the according-to-protocol cohort for persistence (defined as all subjects from the according-to-protocol cohort for immunogenicity with data available at month 18). Safety and reactogenicity were analyzed in the total vaccinated cohort.

The co–primary objectives of the study were to estimate the gE-specific humoral and cellular immune responses 1 month following the third HZ/su vaccination in subjects in the combined ART and ART-naive with high $CD4^+$ T-cell count groups, compared with responses in subjects in the saline group, and to evaluate the safety and reactogenicity of HZ/su in all subjects.

A likelihood-based repeated measures analysis of covariance model was used to evaluate the primary confirmatory objectives. For the high $CD4^+$ T-cell count cohorts, the anti-gE humoral immune response was considered superior in a vaccine group, compared with the saline group, if the lower limit of the 90% confidence interval (CI) of the geometric mean ratio (GMR) between the 2 groups at month 7 was >3. The cell-mediated immune response was considered superior if the lower limit of the 70% CI of the GMR of gE-specific CD4(2+) frequencies at month 7 was >2. All statistical analyses were done using SAS 9.2 (SAS Institute).

RESULTS

Subjects

A total of 123 subjects were randomly assigned and vaccinated. Most subjects were in the ART/high $CD4^+$ T-cell count cohort (94 subjects); the ART/low $CD4^+$ T-cell count and ART-naive cohorts included 14 and 15 subjects, respectively (Figure 1). Most subjects completed the study to month 7 (116 [94.3%]) and the extended follow-up to month 18 (112 [91.1%]), including 67 subjects in the HZ/su group and 45 in the saline group. Mean age at enrollment was 46 years (Table 1), and most subjects were men (94.3%) and white (87.8%).

Cell-mediated Immunity

In the overall study population, the median frequency of gE-specific CD4(2+) T cells increased after vaccination with HZ/su but not with saline (Figure 2 and Supplementary Table 1). At month 7, the frequency of gE-specific CD4(2+) T cells was higher following vaccination with HZ/su than with saline ($P < .0001$). Furthermore, the superiority of HZ/su, compared with saline, was demonstrated in subjects in the combined ART/high $CD4^+$ T-cell count and ART-naive cohorts (GMR, 21.95; 70% CI, 12.97–38.02; $P < .0001$ for the null hypothesis GMR vaccine:saline ≤2). The frequency of CD4(2+) T cells peaked 1 month after the second dose of HZ/su but did not increase further after the third dose. The GMR of the frequencies of gE-specific CD4(2+) T cells at 1 month after dose 3 versus 1 month after dose 2 was 1.04 (95% CI, .82–1.33). The

Table 1. Subject Characteristics

Characteristics	HZ/su (n = 74)	Saline (n = 49)	Total (n = 123)
Age at dose 1, y			
Mean ± SD	46.6 ± 10.68	45.1 ± 11.36	46.0 ± 10.93
Median (range)	47.5 (23–74)	44.0 (26–71)	46.0 (23–74)
Sex			
Female	5 (6.8)	2 (4.1)	7 (5.7)
Male	69 (93.2)	47 (95.9)	116 (94.3)
Ethnicity			
White	66 (89.2)	42 (85.7)	108 (87.8)
African heritage	6 (8.1)	2 (4.1)	8 (6.5)
Other	2 (2.8)	5 (10.2)	7 (5.7)
$CD4^+$ T-cell count at baseline, cells/mm^3, mean ± SD	594.31 ± 273.55	653.88 ± 283.17	. . .
Antiretroviral treatment at baseline			
Nucleoside/nucleotide reverse transcriptase inhibitors	53 (71.6)	32 (65.3)	. . .
Nonnucleoside reverse transcriptase inhibitors	27 (36.5)	16 (32.7)	. . .
Protease inhibitors	30 (40.5)	15 (30.6)	. . .
Others	14 (18.9)	13 (26.5)	. . .
Missing or no value	4 (5.4)	3 (6.1)	. . .

Data are no. (%) of subjects, unless otherwise indicated.

Abbreviations: HZ/su, herpes zoster subunit vaccine candidate; SD, standard deviation.

response profile was comparable for VZV-specific CD4(2+) T-cell frequencies, but the frequencies were lower than for gE.

The proportion of subjects in the HZ/su group with a vaccine-associated cell-mediated immune response following induction with gE increased across doses, with values of 40.0% 1 month after dose 1, 85.7% after dose 2, and 90.0% after dose 3. In the saline group, these proportions were between 8.3% and 16.7%. The cell-mediated immune responses persisted over time, with 64.5% of the subjects in the HZ/su group still having CMI levels above the response threshold 1 year after the last dose, compared with none in the saline group. The VZV-specific cell-mediated immune response rates were lower than the gE-specific ones, with a maximum of 54.5% at month 6 in the HZ/su group.

Humoral Immunity

All subjects in the HZ/su group were seropositive for anti-gE antibodies before vaccination and remained positive thereafter, whereas the proportions ranged between 97.2% and 100% in the saline group at the different time points. In the overall HZ/su group, the anti-gE GMCs increased significantly after the 3 vaccine doses and were maximal 1 month after the third dose (Figure 3 and Supplementary Table 1). One year after the third dose, the anti-gE GMCs remained above the prevaccination concentrations, although they had decreased 60% between month 7 and month 18. In contrast, the anti-gE GMCs did not increase in the saline group after any vaccination. The superiority of HZ/su compared with saline was demonstrated for the gE-specific humoral immune response at month 7 in subjects in the combined ART/high $CD4^+$ T-cell count and ART-naive cohorts (GMR, 46.22; 90% CI, 33.63–63.53; $P < .0001$ for the null hypothesis GMR vaccine:saline ≤3) and for subjects in these 2 cohorts taken separately. The GMR of the anti-gE antibody concentrations at 1 month after the third dose versus 1 month after the second dose was 1.27 (95% CI, 1.11–1.46). In the HZ/su group, the proportions of subjects with anti-gE humoral vaccine responses were between 92.3% and 98.1% at the different time points, whereas they were ≤2.8% in the saline group.

Safety

Pain at the injection site, the most frequent solicited local reaction, was reported by 98.6% of subjects in the HZ/su group and by 12.5% of subjects in the saline group in the 7-day period following vaccinations (Table 2). The proportion of subjects reporting pain after each dose was 81.1%–95.8% in the HZ/su group and 2.6%–8.3% in the saline group (Supplementary Table 2). The most frequent systemic reaction in HZ/su recipients was fatigue (75.3%), followed by myalgia (74.0%) and headache (64.4%). Systemic reactions possibly related to vaccination were reported for 21.9%–60.3% of subjects in the HZ/su group and for 4.2%–16.7% in the saline group. In most cases, solicited local and systemic reactions were transient (median durations, 1–3 days in the HZ/su group) and of mild-to-moderate intensity, with ≤16.4% of subjects in the HZ/su group and ≤8.3% in the saline group reporting severe (grade 3) reactions.

From the first administered dose to 30 days after the last vaccination, 62.2% subjects in the HZ/su group and 73.5% subjects in the saline group reported at least 1 unsolicited AE. Influenza-like illness was the most frequent unsolicited AE in the HZ/su

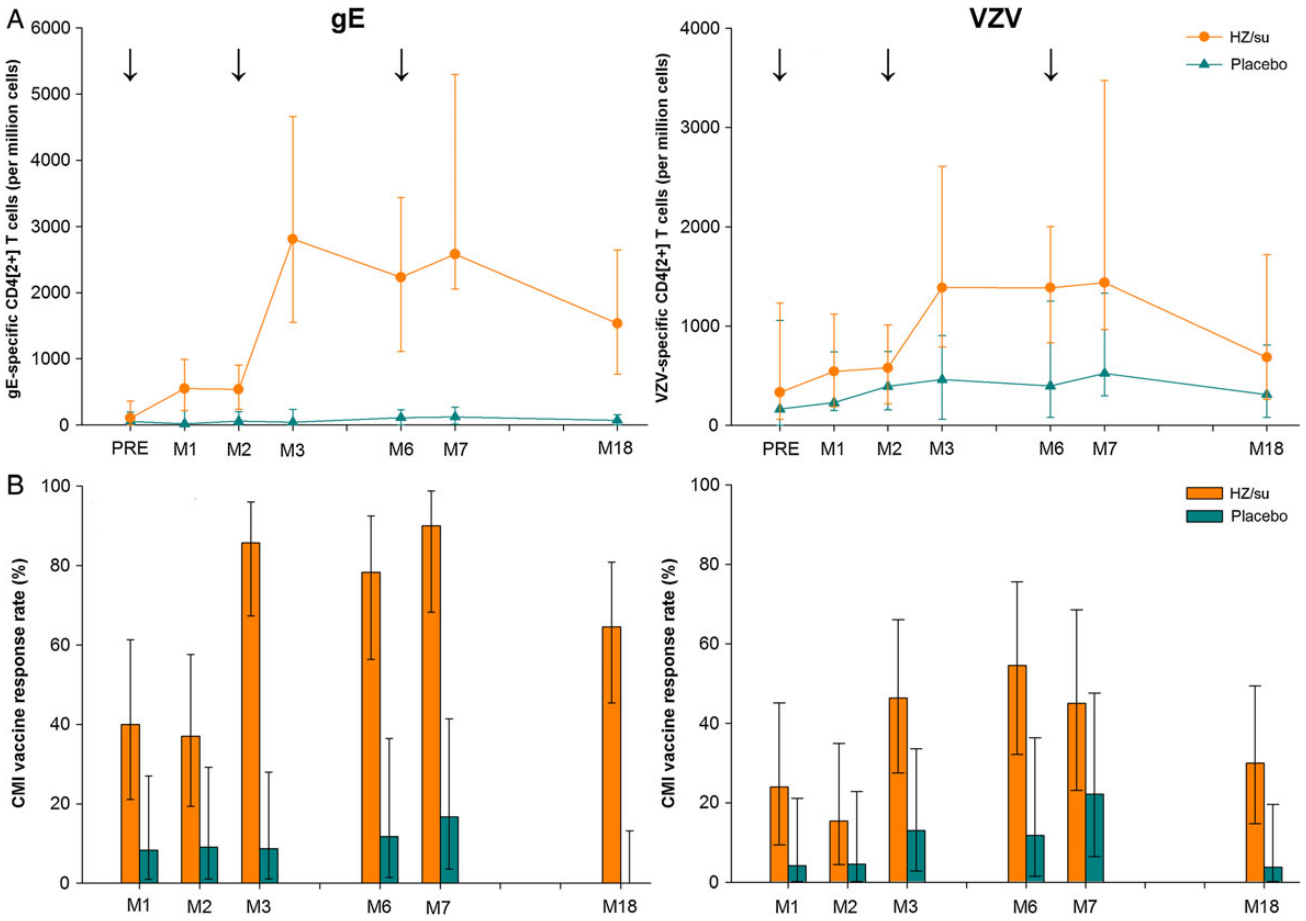

Figure 2. Glycoprotein E (gE)– and varicella-zoster virus (VZV)–specific cell-mediated immune responses. *A*, The median frequencies of $CD4^+$ T cells expressing at least 2 activation markers (CD4[2+]) among CD40 ligand, interleukin 2, tumor necrosis factor α, and interferon γ per 10^6 $CD4^+$ T cells were determined after stimulation with a pool of gE or VZV peptides by intracellular cytokine staining followed by flow cytometry. Error bars indicate interquartile ranges. Arrows indicate vaccinations. *B*, Cell-mediated immune (CMI) vaccine response rate. Data are percentages with 95% confidence intervals (CIs). A CMI vaccine response was defined as a ≥2-fold increase in the frequency of CD4(2+) T cells after induction with gE or VZV, compared with prevaccination levels. Bars indicate means and errors bars indicate 95% CIs. Abbreviation: HZ/su, herpes zoster subunit candidate vaccine.

group and was reported for 6 subjects (8.1%), with 1 report (2.0%) in the saline group. Fever and nasopharyngitis, both reported for 3 subjects (6.1%), were the most frequent unsolicited AE in the saline group. During this period, 4 SAEs were reported (2 each in the HZ/su and saline groups), but none were considered related to vaccination. Over the study period, 7 SAEs were reported in 6 of 74 subjects (8.1%) in the HZ/su group, and 2 SAEs were reported in 2 of 49 (4.1%) in the saline group. None of them were considered by the investigator to be related to vaccination. One subject withdrew because of 2 SAEs (portal hypertension and esophageal variceal hemorrhage) 97 days after the second HZ/su dose. No deaths and no new onset of immune-mediated inflammatory diseases were reported during the study.

Fourteen subjects met protocol-defined criteria for a possible worsening of HIV disease through month 7. Nine subjects (12.2%) in the HZ/su group and 5 (10.2%) in the saline group reported at least 1 event of increased HIV RNA loads or decreased $CD4^+$ T cell counts to prespecified levels. Of these, an increase in HIV RNA load was reported by 3 subjects (4.1%) in the HZ/su group and 1 (2.0%) in the saline group, whereas a >30% decrease in $CD4^+$ T-cell count was reported by 7 subjects (9.5%) in the HZ/su group and 4 (8.2%) in the saline group. Overall, vaccination with HZ/su had no sustained impact on $CD4^+$ T-cell counts or HIV loads, and HZ/su vaccination did not affect mean $CD4^+$ T-cell counts or the proportion of subjects with an HIV RNA load of ≥40 copies/mL at any time through month 18 (data not shown). No clinically relevant changes in hematological or biochemical parameters were found, and no significant changes to ART (due to increased HIV RNA level or decreased $CD4^+$ T-cell count) or AIDS-defining conditions were reported.

One case of HZ was reported during the study. This case occurred in the HZ/su group 83 days after the subject's first and only vaccine dose.

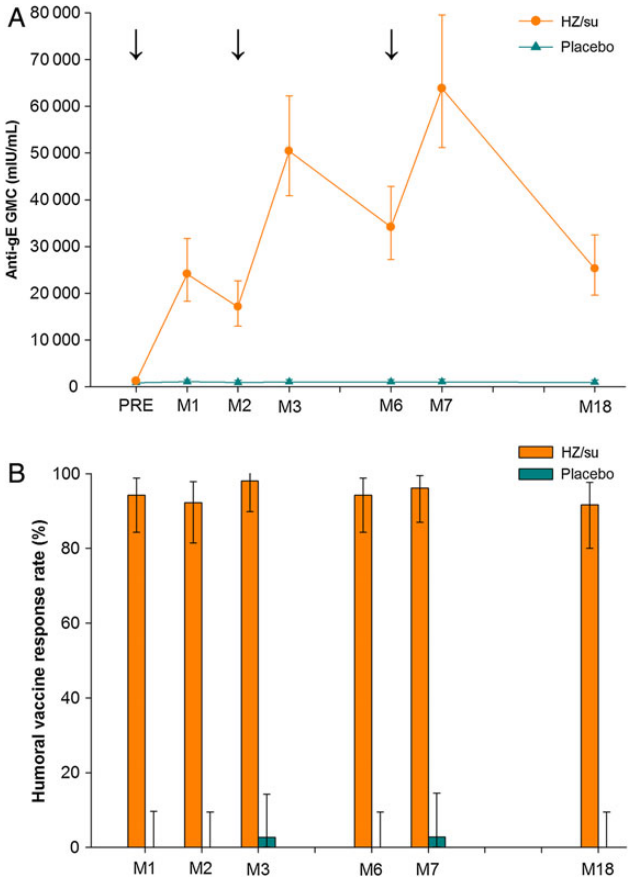

Figure 3. Anti-glycoprotein E (gE) humoral immune response. *A*, Anti-gE antibody concentrations were determined by enzyme-linked immunosorbent assay. Data are geometric mean concentrations (GMCs [mIU/mL]), and error bars indicate 95% confidence intervals (CIs). Arrows indicate vaccinations. *B*, Anti-gE humoral vaccine response rate. Data are percentages with 95% CIs. An anti-gE humoral vaccine response was defined as an anti-gE antibody concentration of ≥4-fold the assay cutoff in initially seronegative subjects and an antibody concentration ≥4-fold the prevaccination antibody concentration in initially seropositive subjects. Abbreviation: HZ/su, herpes zoster subunit candidate vaccine.

Table 2. Incidence of Solicited Local and General Symptoms Reported During the 7-Day Postvaccination Period Overall by Subject

	HZ/su (n = 73)		Saline (n = 48)	
Symptoms	No. (%)	95% CI, %	No. (%)	95% CI, %
Local				
Pain				
Any	72 (98.6)	92.6–100	6 (12.5)	4.7–25.2
Grade 3[a]	12 (16.4)	8.8–27	0 (0)	0–7.4
Redness				
Any	28 (38.4)	27.2–50.5	0 (0)	0–7.4
Grade 3[b]	4 (5.5)	1.5–13.4	0 (0)	0–7.4
Swelling				
Any	20 (27.4)	17.6–39.1	0 (0)	0–7.4
Grade 3[b]	1 (1.4)	0–7.4	0 (0)	0–7.4
General				
Fatigue				
Any	55 (75.3)	63.9–84.7	14 (29.2)	17–44.1
Grade 3[a]	12 (16.4)	8.8–27	4 (8.3)	2.3–20
Vaccine related	41 (56.2)	44.1–67.8	8 (16.7)	7.5–30.2
Gastrointestinal				
Any	28 (38.4)	27.2–50.5	11 (22.9)	12–37.3
Grade 3[a]	2 (2.7)	.3–9.5	1 (2.1)	.1–11.1
Vaccine related	16 (21.9)	13.1–33.1	7 (14.6)	6.1–27.8
Headache				
Any	47 (64.4)	52.3–75.3	15 (31.3)	18.7–46.3
Grade 3[a]	6 (8.2)	3.1–17	2 (4.2)	.5–14.3
Vaccine related	34 (46.6)	34.8–58.6	8 (16.7)	7.5–30.2
Myalgia				
Any	54 (74)	62.4–83.5	9 (18.8)	8.9–32.6
Grade 3[a]	10 (13.7)	6.8–23.8	1 (2.1)	.1–11.1
Vaccine related	44 (60.3)	48.1–71.5	8 (16.7)	7.5–30.2
Shivering				
Any	37 (50.7)	38.7–62.6	5 (10.4)	3.5–22.7
Grade 3[a]	11 (15.1)	7.8–25.4	0 (0)	0–7.4
Vaccine related	29 (39.7)	28.5–51.9	5 (10.4)	3.5–22.7
Fever				
Any[c]	22 (30.1)	19.9–42	3 (6.3)	1.3–17.2
Grade 3[d]	0 (0)	0–4.9	0 (0)	0–7.4
Vaccine related	17 (23.3)	14.2–34.6	2 (4.2)	.5–14.3

Abbreviations: CI, confidence interval; HZ/su, herpes zoster subunit vaccine candidate.

[a] Defined as preventing normal everyday activities.

[b] Defined as a diameter of >100 mm.

[c] Defined as an oral/axillary temperature of ≥37.5°C.

[d] Defined as an oral/axillary temperature of >39°C.

DISCUSSION

This study showed that HZ/su elicits strong gE-specific cell-mediated and humoral immune responses in HIV-infected individuals after 2 and 3 doses and that the responses after dose 3 persist over prevaccination levels at least 1 year after the last vaccination. HZ/su also elicited VZV-specific cell-mediated immune responses but to a lesser extent. Furthermore, although the reactogenicity of HZ/su was substantial, no safety concerns arose in this population.

The primary immunogenicity objective of the study was met. The superiority of HZ/su over saline was demonstrated at month 7 for both humoral and cellular immune responses. These immune responses were comparable to those seen in healthy adults ≥50 years of age [24]. In addition, 1 year after vaccination, the gE-specific CD4(2+) T-cell responses were higher than those seen 1 month after natural HZ [27]. HZ/su is being evaluated as a 2-dose schedule in immunocompetent older adults, but it was not known whether 2 or 3 doses would be required to trigger a strong immune response in HIV-infected individuals. The administration of a third dose

did not show substantial additional benefit over 2 doses in terms of gE-specific humoral and CMI immune responses. These results suggest that, in terms of immunogenicity, a 2-dose schedule (at 0 and 2 months) is appropriate for HIV-infected adults, most of whom were receiving ART and have higher $CD4^+$ T-cell counts, as it is for healthy older adults [22, 24]. Moreover, these results were similar to those obtained in another immunocompromised population, adult autologous HSCT recipients, in whom HZ/su was also strongly immunogenic [28].

Local and systemic reactions were common among HZ/su recipients, and up to 1 of 6 subjects experienced a severe solicited reaction, mostly injection site pain and fatigue. However, these reactions were transient, and no subject withdrew from the study because of a solicited reaction. No vaccination-related SAEs, deaths, or new onsets of immune-mediated inflammatory diseases were reported. Furthermore, HZ/su had no sustained impact on either HIV RNA concentrations or $CD4^+$ T-cell counts over the study period.

Few previous studies have assessed vaccination against HZ in HIV-infected populations. One study evaluated safety and immunogenicity of 2 doses of a live-attenuated varicella vaccine (Varivax; Merck) as a HZ vaccine candidate in HIV-infected adults with $CD4^+$ T-cell counts of >400 cells/μL and HIV RNA loads of < 1000 copies/mL [29]. The vaccine was well tolerated and did not worsen HIV disease, but it was modestly immunogenic. When given as 4 doses in HIV-infected adults with ≤200 $CD4^+$ T cells/mm^3, a heat-inactivated HZ vaccine induced low but significant VZV-specific T-cell and antibody responses and had a favorable safety profile [30].

This study has some limitations. Because of the widespread use of ART in clinical practice in countries participating in the study, we could not enroll many subjects in the ART/low $CD4^+$ T-cell count and ART-naive cohorts. Therefore, because most subjects were in the ART/high $CD4^+$ T-cell count cohort, we pooled subjects of the 3 cohorts for analysis. The analyses in the individual ART/low $CD4^+$ T-cell count and ART-naive/high $CD4^+$ T-cell count cohorts had low statistical power because of the low numbers of subjects enrolled in these cohorts. However, humoral and cellular immune responses were generally higher in the HZ/su groups than in the saline groups in both cohorts. In this study, all subjects were to receive 3 doses of HZ/su; thus, long-term immunopersistence after 2 doses could not be assessed. These data would be of interest because a 2-dose schedule is currently being evaluated in healthy older adults and may also be appropriate for HIV-infected adults.

One clinically confirmed case of HZ occurred in a subject who received 1 dose of HZ/su; however, this study was not designed to assess vaccine efficacy. Furthermore, in the absence of an immunological correlate of protection for HZ [7], correlation between the immune responses described here and the level of clinical protection against HZ cannot be inferred, especially in this immunocompromised population.

In conclusion, this study showed that HZ/su elicits strong gE-specific cellular and humoral immune responses in HIV-infected individuals after 2 doses and that the third dose added little if any immunological advantage. Immunization with an adjuvanted gE subunit vaccine may be an appropriate approach to reduce the burden of HZ and its complications in HIV-infected adults and avoid any risks specific to a live-attenuated vaccine.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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