MAJOR ARTICLE

HIV-1 Virologic and Immunologic Progression and Initiation of Antiretroviral Therapy among HIV-1–Infected Subjects in a Trial of the Efficacy of Recombinant Glycoprotein 120 Vaccine

Peter B. Gilbert,[1] Marta L. Ackers,[3] Phillip W. Berman,[4] Donald P. Francis,[4] Vladimir Popovic,[7] Dale J. Hu,[3] William L. Heyward,[6] Faruk Sinangil,[5] Bryan E. Shepherd,[2] and Marc Gurwith[5]

[1]Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchinson Cancer Research Center, and [2]Department of Biostatistics, University of Washington, Seattle; [3]Centers for Disease Control and Prevention, Atlanta, Georgia; [4]Global Solutions for Infectious Diseases and [5]VaxGen, Brisbane, and [6]Quattro Clinical Research, Oakland, California; [7]Janssen Ortho, Toronto, Ontario, Canada

The first trial of the efficacy of a human immunodeficiency virus (HIV)–1 vaccine was conducted in North America and The Netherlands between 1998 and 2003. This multicenter, randomized, placebo-controlled trial of a recombinant glycoprotein 120 vaccine included 5403 initially HIV-negative volunteers who were monitored for 3 years. The 368 subjects who acquired HIV-1 infection were monitored for 2 years by use of the following postinfection end points: plasma HIV-1 RNA level (viral load), CD4$^+$ lymphocyte count, initiation of antiretroviral therapy (ART), and HIV-1–related clinical outcomes. This article reports the study results that pertain to the effect of vaccination on the postinfection end points. The time until initiation of ART and the time until virologic failure or initiation of ART were similar in the vaccine arm and the placebo arm. The pre-ART viral load and CD4$^+$ lymphocyte count trajectories were also comparable between the groups. Evidently, the vaccine did not affect HIV-1 disease progression.

Two trials of the efficacy of a recombinant glycoprotein 120 (rgp120) vaccine were recently completed [1]. The first trial tested a bivalent subtype B/B vaccine in North America and The Netherlands, and the second trial tested a bivalent subtype B/E vaccine in Thailand. For each trial, the primary objective was to assess whether vaccination reduced the incidence of HIV-1 infection; the secondary objective was to assess whether vaccination delayed disease progression in subjects who acquired HIV-1 infection [2]. For the first trial (VAX004), the results that pertain to primary end points have been reported elsewhere [3]; here, we report the results that pertain to secondary postinfection end points. Many licensed vaccines protect partly or wholly by ameliorating disease, which motivate study of possible disease-modifying effects of the HIV-1 vaccines.

The secondary objective was assessed by comparing outcomes based on initiation of antiretroviral therapy (ART), plasma HIV-1 RNA level (viral load), and CD4$^+$ lymphocyte count between vaccine and placebo recipients. Since viral load and CD4$^+$ lymphocyte count are strong and independent predictors of subsequent progression of clinical HIV-1 disease [4–9], these surrogate end points have been used to support the licensure of antiretroviral drugs [10–13] and will be increasingly useful in the evaluation of candidate HIV-1 vaccines in phase 3 trials [14–15]. Furthermore, in the current era of ART, it is neither feasible nor ethical to study the

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Reprints or correspondence: Dr. Marc Gurwith, VaxGen, 1000 Marina Blvd., Brisbane, CA 94005-1841 (mgurwith@vaxgen.com).

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effect of a vaccine on long-term progression of HIV-1 disease in the absence of treatment, so the analyses of early viral and immunologic events before initiation of ART will become increasingly important.

The rgp120 study vaccine was designed to prevent HIV-1 infection by eliciting anti–HIV-1 neutralizing and binding antibody responses, which it induces in virtually all recipients [2]. Other vaccine candidates under development have focused on the elicitation of $CD8^+$ cytotoxic T lymphocyte (CTL) and $CD4^+$ T helper responses [16, 17]. Several such vaccines have been shown to have the ability to control viremia and prevent disease in nonhuman primate models [18–21]. Although the rgp120 vaccine does not generate $CD8^+$ CTL responses and was not designed specifically to affect disease progression, in most vaccine recipients, it stimulates proliferation of CD4 lymphocytes, which provide a helper function for antibody-producing B cells and $CD8^+$ CTLs [2]. Furthermore, Israel et al. [22] found that macaques immunized with rgp120 vaccine and challenged with SIVmac251 clone BK28 had lower viral loads, compared with control animals, and no disease, and Voss et al. [23] observed a similar result for macaques challenged with SHIV89.6P. These data lead to the hypothesis that a gp120 envelope antigen vaccine could potentially ameliorate HIV-1 disease progression. A preventive HIV-1 vaccine that durably controls viral load could potentially slow the epidemic by reducing infectiousness [24–27], and a vaccine that delays or prevents initiation of ART would extend the AIDS-free period and save treatment and care resources.

SUBJECTS, MATERIALS, AND METHODS

Study design. The VAX004 population included both healthy, HIV-negative, non–injection-drug–using men who have sex with men (MSM) and women at high risk for heterosexual transmission of HIV (18–60 years old). Subjects were randomized in a 2:1 ratio to receive either the vaccine or the placebo. The study vaccine contained 2 rgp120 HIV-1 envelope antigens, derived from 2 different subtype B strains (300 μg each of MN and GNE8 rgp120/HIV-1) (AIDSVAX B/B; VaxGen), that were adsorbed onto 600 μg of alum [28]. The placebo consisted of alum only. Subjects received immunizations at months 0, 1, 6, 12, 18, 24, and 30 and were tested for HIV-1 infection at months 6, 12, 18, 24, 30, and 36 by use of HIV-1 ELISA and confirmatory immunoblot. When subjects received diagnoses of HIV-1 infection, their immunizations were discontinued, and, if they consented, they entered the infected cohort study, in which they were monitored at months 0, <1, 2, 4, 8, 12, 16, 20, and 24 after diagnosis of infection. At each visit, the subject's viral load was determined by the Amplicor 1.0 HIV-1 RNA polymerase chain reaction assay, and his/her $CD4^+$ lymphocyte count was determined by the Coulter system. Whether the subject initiated ART was also recorded. VAX004 was conducted in accordance with ethical requirements [3]. The study was conducted in accordance with the Declaration of Helsinki and local institutional review board requirements and with approval from appropriate regulatory authorities. Written, informed consent was obtained from all subjects.

Statistical methods. Two main analyses of the postinfection end points were prespecified. The first assessed a composite end point defined as virologic failure (viral load >10,000 copies/mL) or initiation of ART, whichever occurred first. A composite end point was constructed to have a clinically relevant interpretation and to be amenable to valid analysis by standard time-to-event methods [14]. The efficacy of the vaccine to prevent the composite end point (VEc) was defined as the percentage reduction (vaccine vs. placebo) in the probability of the composite end point occurring by 12 months after diagnosis of infection. End points occurring during a period of at least 1 year were included to ensure that an observed effect of the vaccine to control viremia would represent moderately durable prevention of the emergence of HIV-1 vaccine resistance mutations [29–31]. VEc was estimated by Kaplan-Meier analysis of the event-free probabilities at 12 months. The effect of the vaccine on 3 additional composite end points—with virologic failure thresholds of 1500, 20,000, or 55,000 copies/mL—was also assessed. The 4 thresholds were chosen both on the basis of the Rakai study, which suggested that persons with viral loads <1500 copies/mL rarely transmit HIV-1 heterosexually [25–26], and on the basis of the Multicenter AIDS Cohort Study (MACS), which demonstrated discrimination of AIDS-progression rates by virologic failure thresholds of 10,000, 20,000, and 55,000 copies/mL in MSM [9]. The MACS population was similar to the VAX004 study population, which included 94.3% MSM.

The second main analysis jointly assessed VEc^{PH} and VEs, where VEc^{PH} is the percentage reduction in the hazard rate (vaccine vs. placebo) of the composite end point (with a virologic failure threshold of 10,000 copies/mL) within 12 months after diagnosis of infection, and VEs is the percentage reduction in the hazard rate (vaccine vs. placebo) of diagnosis of HIV-1 infection within 36 months after randomization. The parameter pair (VEs and VEc^{PH}) was estimated with a joint 95% confidence interval (CI) on the basis of Cox proportional hazards models for 2 periods: (1) between randomization and diagnosis of infection and (2) between diagnosis of infection and the composite end point. This method accounts for correlation in the estimates of VEs and VEc^{PH} [32] and summarizes the aggregate effect of vaccination to prevent infection and the post-infection composite end point. This approach has relatively high statistical power if the vaccine has beneficial effects on both infection and disease progression.

The time to initiation of ART and the longitudinal profiles of pre-ART viral loads and $CD4^+$ lymphocyte counts were also analyzed. Only biomarker values measured before initiation of

ART were included in the analyses, because ART suppresses viremia and maintains $CD4^+$ lymphocytes in most patients [33]; the goal was to evaluate the effect of the vaccine in the absence of ART. Generalized estimating equation (GEE) models [34] were used to test whether mean pre-ART biomarker trajectories differed between the vaccine arm and the placebo arm and to assess the proportion of subjects with pre-ART viral loads <1500 or <400 copies/mL over time. In all GEE models, biomarker trajectories were censored at the time of initiation of ART. These models may give biased results because initiation of ART depends on the responses; multivariable Cox proportional hazards models showed that both pre-ART viral load and pre-ART $CD4^+$ lymphocyte count were significant, independent predictors of initiation of ART, whether entered into the model as the month-1 values or as time-dependent covariates. To minimize possible bias, predictors of initiation of ART were controlled for in the GEE models.

The time-to-event end points were analyzed both in the group of HIV-1–infected subjects and in the entire randomized cohort. The former analyses are important because the effects of the vaccine on HIV-1 pathogenesis are most clearly measured in infected persons. However, these analyses are not intent-to-treat (ITT) analyses and are susceptible to postrandomization selection bias [15]. Therefore, unbiased ITT analyses of the postinfection end points were also conducted for all randomized subjects, and these analyses approximate a classical assessment of the efficacy of the vaccine to prevent clinically significant disease [35]. For analyses of the randomized cohort, subjects who did not experience the postinfection end point within 36 months of randomization were censored at 36 months, and, for analyses of the infected subcohort, subjects who did not experience the postinfection end point within 24 months of randomization were censored at 24 months. Viral load is highly variable during the first several weeks after acquisition of HIV-1 infection [9, 36–38]. On the basis of the semiannual HIV-1 testing schedule, on average, HIV-1 infection was detected 3 months after transmission, and a small fraction of infected subjects may have had a viral load at month <1 that was determined during the acute phase. To minimize the effect of the extremely wide variability of acute viral loads, values for month <1 were not used for determination of the composite end points. Therefore, the composite end points were registered at the earliest date of initiation of ART or virologic failure on the basis of a viral load measurement at the month-1 visit or later.

At baseline, standard questionnaires were administered to assess self-reported risk behavior during the previous 6 months. On the basis of multivariable Cox regression analysis, 9 baseline behavioral variables were found to be independent predictors of risk of infection (table 1). Behavioral risk was categorized into low, medium, and high, which were defined as the presence of 0, 1–3, or >3 of the 9 risk factors, respectively [3].

Time-to-event end points were assessed by use of Kaplan-Meier curves and log-rank tests. All analyses included all subjects regardless of the number of immunizations received; results were similar for "fully immunized" subjects who received the month-0, -1, and -6 immunizations before HIV-1 infection. All P values are 2-sided, and no adjustments were made for multiple testing, except where indicated.

RESULTS

Follow-up and characteristics of infected subjects. Figure 1 illustrates the number of subjects, by study arm, in the different stages of the trial. Of the 5403 randomized subjects, 368 acquired HIV-1 infection: 241 (6.7%) of 3598 vaccine recipients and 127 (7.0%) of 1805 placebo recipients. Of the 368 infected subjects, 347 (225 vaccine recipients and 122 placebo recipients) were enrolled into the infected cohort and could be evaluated for postinfection end points. Among these subjects, the median length of follow-up was 19.7 months. The rate of dropout did not differ by study arm ($P = .79$, log-rank test). Data on subjects were unblinded on 1 June 2003, after which no further visits were scheduled. Of the 335 subjects diagnosed with HIV before 1 June 2002 (all of whom should have reached the 12-month visit), 269 (80%) had a 12-month visit (176 vaccine recipients and 93 placebo recipients). Table 1 summarizes the characteristics of the 347 infected subjects. Most subjects were men (98.3%); were white, non-Hispanic (83.9%); and had medium (62.3%) or high (22.3%) risk at baseline. Ages were predominantly 26–50 years, and the education level was high (60.5% college graduates). HIV-1 infections were diagnosed between 1998 and 2002, with the majority (72.3%) occurring in 2000–2001, and 271 subjects (78.1%) received the month-0, -1, and -6 immunizations before infection. Only 5 (1.4%) of the 347 infected subjects (all vaccine recipients) and 108 (2.0%) of the uninfected subjects (70/3598 vaccine recipients [1.9%] and 38/1805 placebo recipients [2.1%]) reported receiving postexposure prophylaxis.

Effect of the vaccine on initiation of ART and virologic failure. Figure 2 shows Kaplan-Meier curves of the time to initiation of ART and the time to the composite end point (initiation of ART or virologic failure), with a virologic failure threshold of 10,000 copies/mL. For the infected cohort, 99 (44.0%) of 225 vaccine recipients and 53 (43.4%) of 122 placebo recipients started ART within 24 months; the rate of ART was similar among groups ($P = .61$, log-rank test). A total of 183 (81.3%) of 225 vaccine recipients and 96 (78.7%) of 122 placebo recipients reached the composite end point within 24 months; the rates were similar ($P = .48$, log-rank test). In the randomized cohort, there was a trend toward a longer time to initiation of ART in vaccine recipients, with 59 (1.6%) of 3598

Table 1. Characteristics of the HIV-1–infected subjects in VAX004 by study arm.

Characteristic	Vaccine (n = 225)	Placebo (n = 122)	Total[a] (n = 347)
Geographic region[b]			
Midwest	22 (9.8)	21 (17.2)	43 (12.4)
The Netherlands	4 (1.8)	1 (0.8)	5 (1.4)
Northeast	49 (21.8)	35 (28.7)	84 (24.2)
South	43 (19.1)	17 (13.9)	60 (17.3)
Southwest	49 (21.8)	19 (15.6)	68 (19.6)
West Coast	58 (25.8)	29 (23.8)	87 (25.1)
Sex at birth			
Male	223 (99.1)	118 (96.7)	341 (98.3)
Female	2 (0.9)	4 (3.3)	6 (1.7)
Age, years			
18–25	30 (13.3)	17 (13.9)	47 (13.5)
26–30	48 (21.3)	23 (18.9)	71 (20.5)
31–40	96 (42.7)	54 (44.3)	150 (43.2)
41–50	39 (17.3)	23 (18.9)	62 (17.9)
>50	12 (5.3)	5 (4.1)	17 (4.9)
Race/ethnicity			
White, non-Hispanic	197 (87.6)	94 (77.0)	291 (83.9)
Black, non-Hispanic	5 (2.2)	9 (7.4)	14 (4.0)
Hispanic	13 (5.8)	9 (7.4)	22 (6.3)
Asian/Pacific Islander	3 (1.3)	3 (2.5)	6 (1.7)
Other	7 (3.1)	7 (5.7)	14 (4.0)
Education			
Less than high school	3 (1.3)	3 (2.5)	6 (1.7)
High school graduate	84 (37.3)	47 (38.5)	131 (37.8)
College graduate	98 (43.6)	51 (41.8)	149 (42.9)
Advanced degree	40 (17.8)	21 (17.2)	61 (17.6)
Baseline risk score[c]			
Low (score 0)	28 (12.4)	10 (8.2)	38 (15.4)
Medium (score 1–3)	167 (74.2)	87 (71.3)	154 (62.3)
High (score >3)	30 (13.3)	25 (20.5)	55 (22.3)
Calendar time at diagnosis of infection			
1998–1999	27 (12.0)	17 (13.9)	44 (12.7)
1 January 2000–30 June 2000	39 (17.3)	29 (23.8)	68 (19.6)
1 July 2000–31 December 2000	52 (23.1)	22 (18.0)	74 (21.3)
2001	73 (32.4)	36 (29.5)	109 (31.4)
2002	34 (15.1)	18 (14.8)	52 (15.0)
Fully immunized[d]			
No	49 (21.8)	27 (22.1)	76 (21.9)
Yes	176 (78.2)	95 (77.9)	271 (78.1)
Postexposure prophylaxis			
No	220 (97.8)	122 (100)	342 (98.6)
Yes	5 (2.2)	0 (0.0)	5 (1.4)

NOTE. Data are no. (%) of subjects.

[a] A total of 347 of 368 infected subjects were enrolled into the postinfection phase of the trial.

[b] Midwest: Illinois, Indiana, Minnesota, Ohio, and Wisconsin; Northeast: Washington, DC, Massachusetts, Maryland, New Jersey, New York, Ontario, Pennsylvania, Quebec, and Rhode Island; South: Alabama, Florida, Georgia, Louisiana, Missouri, North Carolina, and Puerto Rico; Southwest: Arizona, Colorado, New Mexico, Nevada, Oklahoma, and Texas; West Coast: British Columbia, California, Hawaii, and Oregon.

[c] The baseline risk score is the no. of the following risk factors that, at baseline, a subject reported to have had during the past 6 months: (1) unprotected receptive anal sex with an HIV-positive male partner, (2) unprotected unassertive anal sex with an HIV-positive male partner, (3) unprotected receptive anal sex with an HIV-negative male partner, (4) $\geqslant$5 episodes of unprotected receptive anal sex with a male partner whose HIV-1 status was unknown , (5) $\geqslant$10 sex partners, (6) anal herpes, (7) hepatitis A, (8) use of poppers (nitrite inhalants), and (9) use of amphetamines [3].

[d] An HIV-infected subject was fully immunized if he/she received the month-0, -1, and -6 immunizations and was infected after the month-6 immunization.

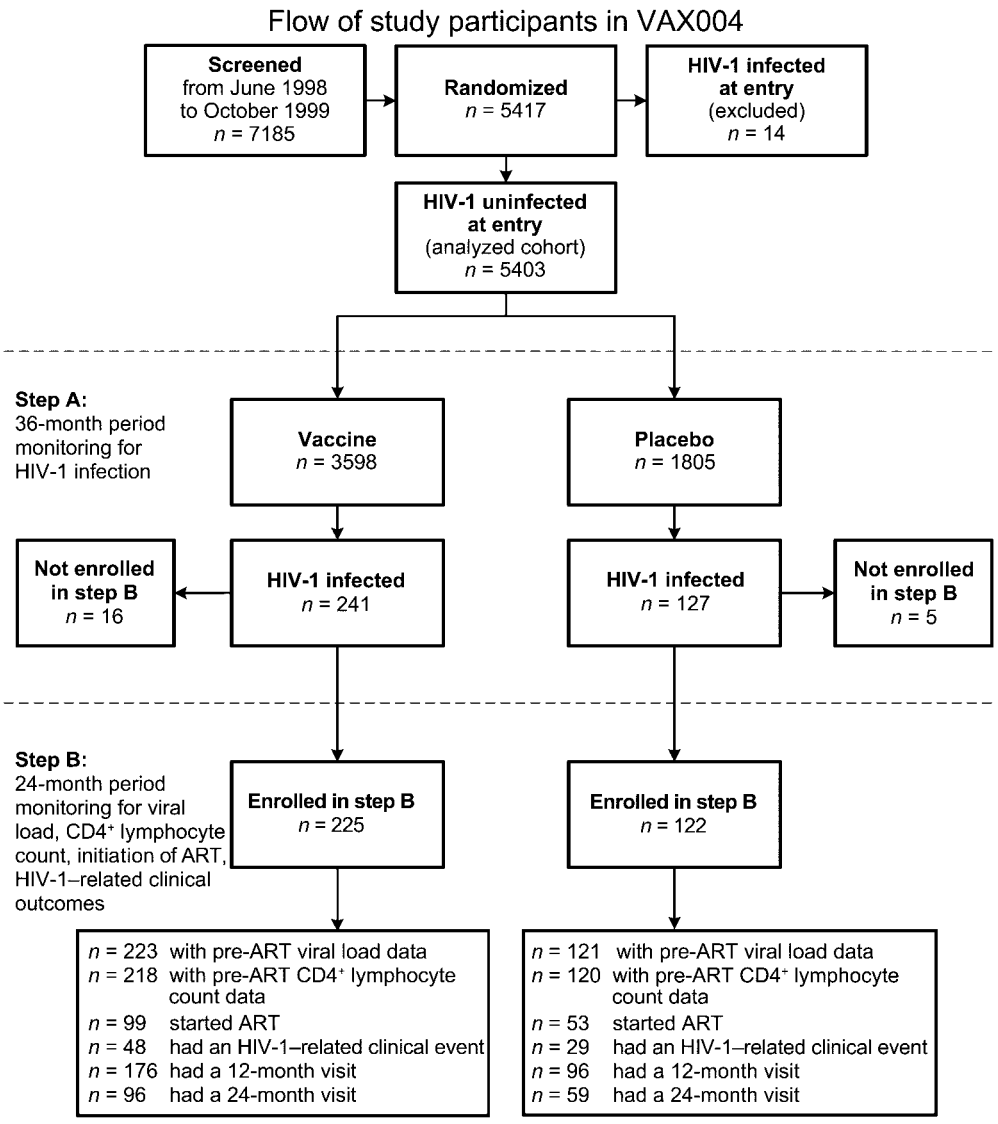

Figure 1. Flowchart of subjects in the VAX004 phase 3 trial of the efficacy of HIV-1 vaccine

vaccine recipients and 42 (2.3%) of 1805 placebo recipients starting ART within 36 months ($P = .07$, log-rank test), but there were no differences in the rate of the composite end point (163/3598 vaccine recipients [4.5%] and 89/1805 placebo recipients [4.9%]) ($P = .43$, log-rank test).

For the infected cohort, for the virologic failure thresholds of 1500, 10,000, 20,000, and 55,000 copies/mL, respectively, VEc was estimated as −3.3% (95% CI, −9.2% to 2.6%), 1.0% (95% CI, −10.8% to 12.9%), 2.8% (95% CI, −10.8% to 16.5%), and 0.3% (95% CI, −19.5% to 20.1%); a simulation procedure was used to compute the 4 CIs such that they included all 4 true VEc parameters simultaneously with ⩾0.95 probability. By use of a Cox model controlling for region, sex, age, race, education, baseline risk score, and calendar time at diagnosis of infection (table 1), VEc^{PH} with a virologic failure threshold of 10,000 copies/mL was estimated as −8.1% (95% CI, −40.8% to 17.1%) ($P = .57$).

Effect of the vaccine on pre-ART viral loads and CD4⁺ lymphocyte counts. Figure 3 shows the viral loads and $CD4^+$ lymphocyte counts that were measured before initiation of ART. On average, infected subjects had 4.5 pre-ART viral load values available (range, 0 [3 subjects] to 10 values). Of the 1657 total values, 302 (18.2%) were outside the quantifiable range (400–750,000 copies/mL) of the assay: 259 values were <400 copies/mL, and 43 values were >750,000 copies/mL. Values below and above the quantification limit were prespecified at 399 and 750,000 copies/mL, respectively. On average, infected subjects had 4.0 pre-ART $CD4^+$ lymphocyte counts available (range, 0 [9 subjects] to 9 counts). Pooled over the study arms, at months <1, 1, 2, 4, 8, 12, 16, 20, and 24, the median $\log_{10}$

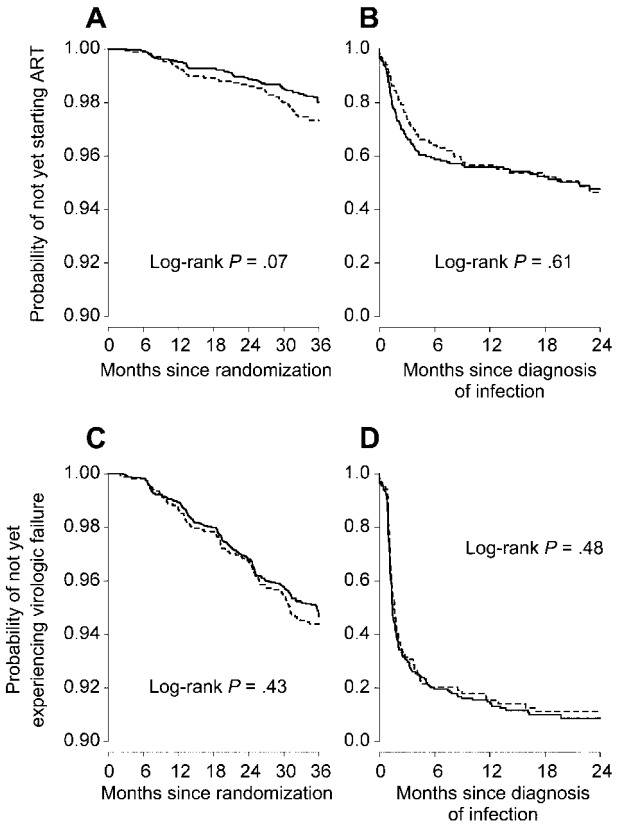

Figure 2. Kaplan-Meier curves of the time between randomization and initiation of antiretroviral therapy (ART) *(A),* the time between diagnosis of infection and initiation of ART *(B),* the time between randomization and the composite end point (viral load >10,000 copies/mL or initiation of ART) *(C),* and the time between diagnosis of infection and the composite end point *(D).* The vaccine group curves are indicated by solid lines, and the placebo group curves are indicated by dashed lines.

pre-ART viral loads were 4.37, 4.17, 3.94, 3.99, 4.27, 4.23, 4.29, 4.21, and 4.14 copies/mL, respectively, and the median pre-ART $CD4^+$ lymphocyte counts were 596, 602, 586, 606, 552, 557, 546, 506, and 492 cells/mm^3, respectively. At the month-2 visit, the mean $\log_{10}$ pre-ART (set-point) viral load was 4.33 copies/mL in the vaccine arm and 4.26 copies/mL in the placebo arm (mean difference, 0.07 copies/mL [95% CI, −0.18 to 0.33 copies/mL]), and the mean pre-ART $CD4^+$ lymphocyte count was 635 cells/mm^3 in the vaccine arm and 609 cells/mm^3 in the placebo arm (mean difference, 26 cells/mm^3 [95% CI, −90 to 40 cells/mm^3]). A sensitivity analysis of the effect of the vaccine on the pre-ART viral load at months <1, 1, and 2, an analysis that accounted for the assay censoring of viral load values and for possible selection bias, further supported the inference that the vaccine had no significant effect on early viral load [39].

GEE models were fit with and without adjustment for the covariates region, sex, age, race, education, baseline risk score, and calendar time at diagnosis of infection. The mean pre-ART viral load trajectories were comparable between the study arms (unadjusted $P = .81$; adjusted $P = .80$). Linear mixed-effects models that accounted for the quantification-limit censoring of viral loads [40] and that controlled for time-dependent $CD4^+$ lymphocyte counts, as well as for other covariates, also showed no differences. GEE models for the pre-ART $CD4^+$ lymphocyte trajectories showed no differences between study arms (unadjusted $P = .43$; adjusted $P = .77$).

The ability of the vaccine to control pre-ART viral load to <1500 or <400 copies/mL was also assessed. At months 1, 4, 12, and 24, respectively, 22 (17.3%), 16 (13.8%), 10 (13.0%), and 4 (10.3%) vaccine recipients versus 13 (18.6%), 10 (14.5%), 5 (10.2%), and 3 (13.0%) placebo recipients had pre-ART viral loads <1500 copies/mL, and 11 (8.7%), 8 (6.9%), 6 (7.8%), and 4 (10.3%) vaccine recipients versus 9 (12.9%), 3 (4.4%), 3 (6.1%), and 2 (8.7%) placebo recipients had pre-ART viral loads <400 copies/mL. On the basis of binary GEE models with or without covariate adjustment, there were no significant differences in the proportion of subjects with viral loads suppressed to <1500 or <400 copies/mL between the study arms ($P > .20$).

Joint assessment of the effect of the vaccine on HIV-1 infection and HIV-1 disease progression. The parameter pair VEs and VEc^{PH} were estimated as 8.5% and 10.2%, respectively; the joint 95% confidence region (CR) is depicted in figure 4. The CR mostly contained the null-hypothesis region, supporting VEs ≤30% and VEc^{PH} ≤40%.

HIV-1 disease progression, AIDS, and death. Forty-eight (21.3%) of 225 infected vaccine recipients and 29 (23.8%) of 122 infected placebo recipients progressed to an HIV-related clinical outcome, as defined by category B or C in the 1993 US case definitions [41]. The time to the first HIV-related clinical outcome was comparable between the study arms ($P = .95$, log-rank test). Of the 77 subjects with a clinical outcome, 48 (30/225 vaccine recipients [13.3%] and 18/122 placebo recipients [14.8%]) had a category B event as their first clinical outcome. These events were diarrhea for >30 days (18 vaccine recipients and 13 placebo recipients), neuropathy (5 vaccine recipients and 1 placebo recipient), lymphadenopathy (2 vaccine recipients and 4 placebo recipients), oral candidiasis (4 vaccine recipients), and fever for >30 days (1 vaccine recipient). In addition, 29 subjects had a category C event (an AIDS-defining illness) [41] as their first clinical outcome: $CD4^+$ lymphocyte count <200 cells/mm^3 (6 vaccine recipients and 6 placebo recipients), aphthous stomatitis for >30 days (5 vaccine recipients and 1 placebo recipient), clinical herpes for >30 days (4 vaccine recipients and 1 placebo recipient), pneumonia (1 vaccine recipient and 3 placebo recipients), Kaposi sarcoma (1 vaccine recipient), and fungal infection (1 vaccine recipient). No infected subjects died during follow-up.

Subgroup assessments. As reported in the study by the

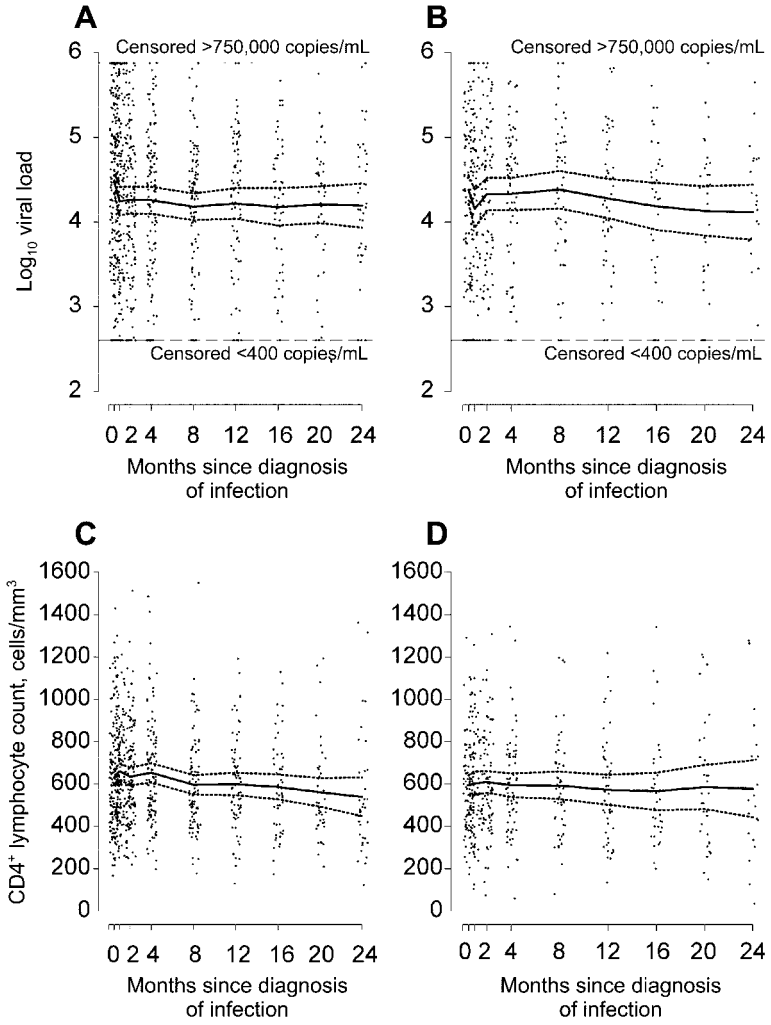

Figure 3. Pre–antiretroviral therapy (ART) measurements of $\log_{10}$ viral loads for the vaccine group *(A)* and the placebo group *(B)* and $CD4^+$ lymphocyte counts for the vaccine group *(C)* and the placebo group *(D)*. The data are grouped by visits, with jittering to aid visibility. On the basis of the visit-grouped data, for each study arm and visit at <1, 1, 2, 4, 8, 12, 16, 20, and 24 months, the mean value and the 95% confidence interval (CI) were computed on the basis of the sample average and sample variance. The solid lines connect the mean estimates across the visits, and the dashed lines connect the 95% CIs. For each subject, at most 1 value for each visit was used. In the few cases in which a subject had multiple values determined at 1 visit, a single value was selected; for viral loads, the largest value was used, and, for $CD4^+$ lymphocyte counts, the smallest value was used.

rgp120 HIV Vaccine Study Group [3], exploratory analyses suggested that VEs may have varied between whites and nonwhites and between subjects with low, medium, and high baseline risk scores. The analyses of the postinfection end points were repeated within race/ethnicity and behavioral risk subgroups, and the results were comparable to those for the overall cohort, supporting the inference that the vaccine had no effect on HIV-1 disease progression (data not shown).

DISCUSSION

The effect of the vaccine on several end points based on initiation of ART, viral load, $CD4^+$ lymphocyte count, and HIV-1–related clinical events were assessed over the course of a 2 year follow-up period after diagnosis of HIV-1 infection in VAX004 study subjects who acquired HIV-1 infection while enrolled in the trial. The vaccine was not observed to have an effect on any of the postinfection end points, and the results of the study strongly support the inference that the vaccine had neither beneficial nor harmful effects on HIV-1 disease progression. There was concern that the vaccine could possibly exacerbate disease, on the basis of in vitro HIV-1 studies [42–44] and studies demonstrating disease enhancement by envelope-based non-HIV vaccines [45–51]. An important result of VAX004 is that the rgp120 vaccine did not enhance HIV-1 disease progression.

The first event of virologic failure or initiation of ART (the

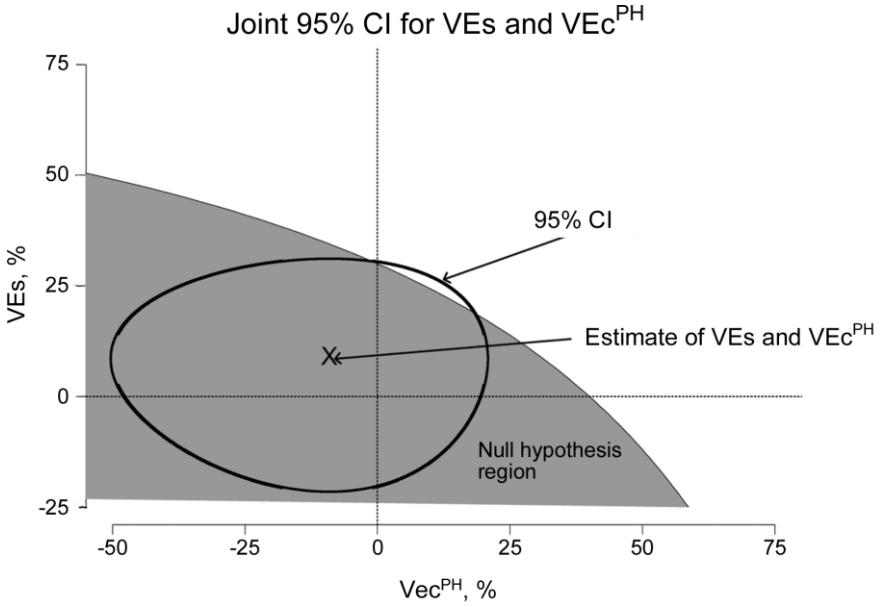

Figure 4. Cox proportional hazards–based estimates of VEs and VEc^{PH} (indicated by "X"), with a joint 95% confidence region (CR) for VEs and VEc^{PH} *(solid lines).* VEs is the efficacy of the vaccine to prevent infection by the month-36 postrandomization visit (VEs = [1 − relative risk] × 100%), and VEc^{PH} is the efficacy of the vaccine to prevent the composite end point (viral load >10,000 copies/mL or initiation of antiretroviral therapy) by the month-12 postinfection visit (VEc^{PH} = [1 − relative risk] × 100%). The shaded area marked "null hypothesis region" indicates the set of VEs and VEc^{PH} values prespecified as clinically nonsignificant.

composite end point) was used as a main end point for measuring the effect of the vaccine on HIV-1 disease progression. Inferences with respect to the composite end point will be more clearly interpretable in efficacy trials that use standardized initiation-of-ART guidelines [14]. Standardized guidelines were not used in VAX004, and, therefore, the results must be interpreted carefully. Of the 279 total composite end points registered during the trial, 208 (74.6%) were due to virologic failure, and 71 (25.4%) were due to initiation of ART before a viral load >10,000 copies/mL had been reached. The $CD4^+$ lymphocyte count for 61 (85.9%) of these 71 subjects never dropped below 350 cells/mm^3; therefore, these 61 subjects started ART prematurely, on the basis of the 2002 ART guidelines [33]. Consequently, 61 (21.9%) of the 279 composite end points can be viewed as possible noise that could have attenuated a real effect of the vaccine. When these 61 events were excluded, the composite end point rates were still comparable between the vaccine arm (136/225 [60.4%]) and the placebo arm (82/122 [67.2%]), lending robustness to the inference that the vaccine had no significant effect. Inferences with respect to the composite end point will be more clearly interpretable in efficacy trials that use standardized initiation-of-ART guidelines. Subjects infected earlier in the trial (1998–1999) tended to start ART more quickly than did subjects infected later (2001–2002) ($P < .0001$; data not shown). This pattern reflects the evolving recommendations for when to start ART, from the prevailing recommendation to start ART near the beginning of the trial, to "hit early and hard" [52], to the 2002–2003 recommendation to defer ART until the emergence of clinical symptoms, low $CD4^+$ lymphocyte count, or high viral load [33, 53]. The more-recent recommendations will facilitate analyses of forthcoming trials of the efficacy of HIV-1 vaccines, since, for most infected trial subjects, fairly long ART-free periods are necessary for reliable assessments of the durability of the effects of the vaccine (in the absence of ART) on viral load and other biomarker end points.

In VAX004, a limitation of the assessment of the effects of the vaccine on HIV-1 disease progression is that the results are based on surrogate end points that have not been validated as reliable replacements for the clinical end points of interest (AIDS-defining illnesses and secondary transmission). Surrogacy of these end points for therapies may not translate into surrogacy for vaccines, due to different mechanisms of efficacy. There was low statistical power to assess the effect of the vaccine on progression to AIDS, since only 77 (22.2%) of 347 infected subjects experienced an HIV-related clinical event within the relatively short follow-up period. Although it is not possible to verify that the absence of an effect of the vaccine on the early biomarker surrogate end points implies the absence of an effect of the vaccine on progression to AIDS, this seems likely, on the basis of previous natural-history studies [7–10]. In future trials, to allow identification of trends of effects of the vaccine on clinical end points and to help interpret observed effects of the vaccine on biomarker end points, it may be important to

collect data on a variety of clinical end points over the course of several years [54].

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