MAJOR ARTICLE

Randomized, Double-Blind, Placebo-Controlled Efficacy Trial of a Bivalent Recombinant Glycoprotein 120 HIV-1 Vaccine among Injection Drug Users in Bangkok, Thailand

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Background. In Thailand, phase 1/2 trials of monovalent subtype B and bivalent subtype B/E (CRF01_AE) recombinant glycoprotein 120 human immunodeficiency virus type 1 (HIV-1) vaccines were successfully conducted from 1995 to 1998, prompting the first HIV-1 vaccine efficacy trial in Asia.

Methods. This randomized, double-blind, placebo-controlled efficacy trial of AIDSVAX B/E (VaxGen), which included 36-months of follow-up, was conducted among injection drug users (IDUs) in Bangkok, Thailand. The primary end point was HIV-1 infection; secondary end points included plasma HIV-1 load, CD4 cell count, onset of acquired immunodeficiency syndrome–defining conditions, and initiation of antiretroviral therapy.

Results. A total of 2546 IDUs were enrolled between March 1999 and August 2000; the median age was 26 years, and 93.4% were men. The overall HIV-1 incidence was 3.4 infections/100 person-years (95% confidence interval [CI], 3.0–3.9 infections/100 person-years), and the cumulative incidence was 8.4%. There were no differences between the vaccine and placebo arms. HIV-1 subtype E (83 vaccine and 81 placebo recipients) accounted for 77% of infections. Vaccine efficacy was estimated at 0.1% (95% CI, −30.8% to 23.8%; $P = .99$, log-rank test). No statistically significant effects of the vaccine on secondary end points were observed.

Conclusion. Despite the successful completion of this efficacy trial, the vaccine did not prevent HIV-1 infection or delay HIV-1 disease progression.

The Thai HIV-1 epidemic began in the late 1980s, with a rapid introduction of HIV-1 subtype B among injection drug users (IDUs) followed by a larger epidemic of sexually transmitted subtype E (later designated as CRF01_AE) [1]. In 1988, the prevalence of HIV-1 infection among IDUs in Bangkok increased from <1% to ~40% [2]. Thailand has been successful in controlling the heterosexual spread of HIV-1, with estimated new infections decreasing from 143,000 in 1991 to 20,000 in 2004 [3]. This reduction reflects Thailand's strong commitment to confronting the epidemic and implementing prevention strategies. Thailand's first National Plan for HIV Vaccine Development and Evaluation was established in 1993, with a revision in 1997 [4]. The recombinant (r) gp120 vaccine was selected for evaluation on the basis of safety and immunogenicity profiles in humans [5–7]. A phase 1/2 trial of a monovalent subtype B rgp120 vaccine among IDUs in Bangkok was successfully conducted in 1995–1996 [8], which was followed by a similar trial of a bivalent subtype B/E rgp120 vaccine in 1998 [9]. These trials demonstrated that rgp120 was safe and immunogenic. In parallel, 1209 HIV-1–negative IDUs were enrolled in a vaccine preparatory study, which documented an HIV-

Received 28 February 2006; accepted 28 July 2006; electronically published 3 November 2006.

Potential conflicts of interest: none reported.

Financial support: VaxGen, Inc.

Clinical Trial registration number: 36424.

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The Journal of Infectious Diseases 2006; 194:1671–71

0022-1899/2006/19412-0007$15.00

1 incidence of 5.8 infections/100 person-years, with 79% being subtype E infections and 21% being subtype B infections [10]. Follow-up rates were 88.2% at 12 months and 75.9% at 24 months. Fifty percent of volunteers reported a definite willingness to participate in HIV-1 vaccine trials [11]. On the basis of these data, a phase 3 HIV-1 vaccine efficacy trial of AIDSVAX B/E (VaxGen) was conducted. In the present report, we describe the trial methodology, conduct, and outcomes.

VOLUNTEERS, MATERIALS, AND METHODS

Study Design

This randomized, double-blind, placebo-controlled vaccine efficacy trial was conducted among IDUs attending 17 Bangkok Metropolitan Administration (BMA) drug-treatment clinics. These clinics provide methadone detoxification (45 days) and methadone maintenance (daily) treatment for ~8000 heroin addicts per year [12]. Eligibility criteria were age of 20–60 years, drug injection during the past year, being negative for HIV-1 by ELISA at screening and baseline, and provision of written consent after passing 2 trial comprehension tests. Female volunteers could not be pregnant at baseline, could not be breastfeeding, and were required to commit to contraceptive use during the study. A computer-generated block randomization list, stratified by clinic, was designed to satisfy a 1:1 vaccine: placebo ratio.

Risk Counseling and Assessment

At each visit, volunteers were counseled to eliminate HIV risk behavior, including drug injection, needle sharing, and unprotected sexual intercourse. Male condoms and bleach to clean injection equipment were provided free of charge.

Questionnaires to assess risk behavior and social harms related to trial participation were administered every 6 months. If a study-related social harm was reported, such as denial of health insurance or discrimination because of HIV infection, an intervention was made to resolve the harm, and follow-up was conducted [13].

Vaccine and Placebo Preparations

AIDSVAX B/E contains 2 rgp120 HIV-1 envelope antigens: 1 from a CXCR4-dependent laboratory-adapted subtype B strain (MN), and 1 from a CCR5-dependent primary subtype CRF01_AE isolate (A244), each produced from stable, transfected CHO cell lines [14, 15]. A244 was isolated in northern Thailand in 1990 [16, 17]. Purified protein (300 μg of MN and 300 μg of A244) was adsorbed onto a total of 600 μg of alum. Southeast Asian subtype E strains have been determined to be CRF01_AE with subtype A–like *gag, pol,* and *env* gp41 regions, but the *env* gp120 has been characterized as belonging entirely to an HIV-1 subtype E lineage. The subtype B strain MN used in the vaccine is similar to but distinct from subtype B′ strains circulating in Thailand [18, 19]. The placebo contained only alum adjuvant.

Vaccine Administration and Outcome Measurements

Vaccine or placebo was injected intramuscularly at months 0, 1, 6, 12, 18, 24, and 36. At each visit, adverse events were assessed and blood was collected, to determine vaccine antibody response and HIV-1 status by ELISA and immunobloting. The presence of 2 bands other than gp120 or gp160 was required for an immunoblot to be considered confirmatory. To estimate the date of HIV-1 infection, nucleic acid–based amplification testing (NAT) was performed in volunteers with serologic evidence of incident infection. The date of infection was estimated as follows: if HIV-1 RNA was undetectable by NAT in the last seronegative serum specimen, then the date of infection was estimated as the midpoint of the dates for last negative and first positive ELISA/immunoblot. Otherwise, the infection date was estimated as the date for earliest specimen with detectable HIV-1 RNA.

HIV-1 infection was determined at the BMA laboratory by use of the Genetic Systems–Biorad ELISA and Western blot kits. At a VaxGen contract laboratory, specimens immediately collected before the first seropositive sample were assayed for the presence of HIV-1 RNA by NAT (Procleix HIV-1 discriminatory assay; Chiron). Volunteers with incident HIV-1 infection were followed up at months <1, 1, 2, 4, 8, 12, 16, 20, and 24. At each visit, blood was collected for determination of plasma HIV-1 RNA load by reverse-transcription polymerase chain reaction (RT-PCR) (Amplicor HIV-1 Monitor; version 1.5; Roche Diagnostic Systems), and CD4 and CD8 cell counts were done by 2-color flow cytometry (FACScan; Becton Dickinson) in accordance with US Centers for Disease Control and Prevention (CDC) guidelines [20]. These assays were performed at the Thailand Ministry of Public Health (MOPH)–CDC Collaboration laboratory with EDTA-anticoagulated blood. At the VaxGen laboratory, 5 assays were used to measure rgp120 antibody responses: an ELISA for antibody that blocks the binding of A244 to the CD4 coreceptor; an ELISA for anti–A244 V2; an ELISA for anti–A244 V3; an ELISA for anti–gp120 MN/A244 (mixed) binding antibodies; and an ELISA for MN neutralization [21, 22]. Specimens collected at the last immunization visit before the first seropositive sample and 2 weeks after the last immunization visit were assayed for this purpose. In addition, assays were performed on random samples of specimens collected at the time of all immunizations and 2 weeks after immunization from 10% of uninfected vaccine (n = 115) and 1% of uninfected placebo (n = 12) recipients.

HIV-1 subtype determination was performed by VaxGen. Viral RNA and DNA were isolated from 0.5–1.0 mL of frozen

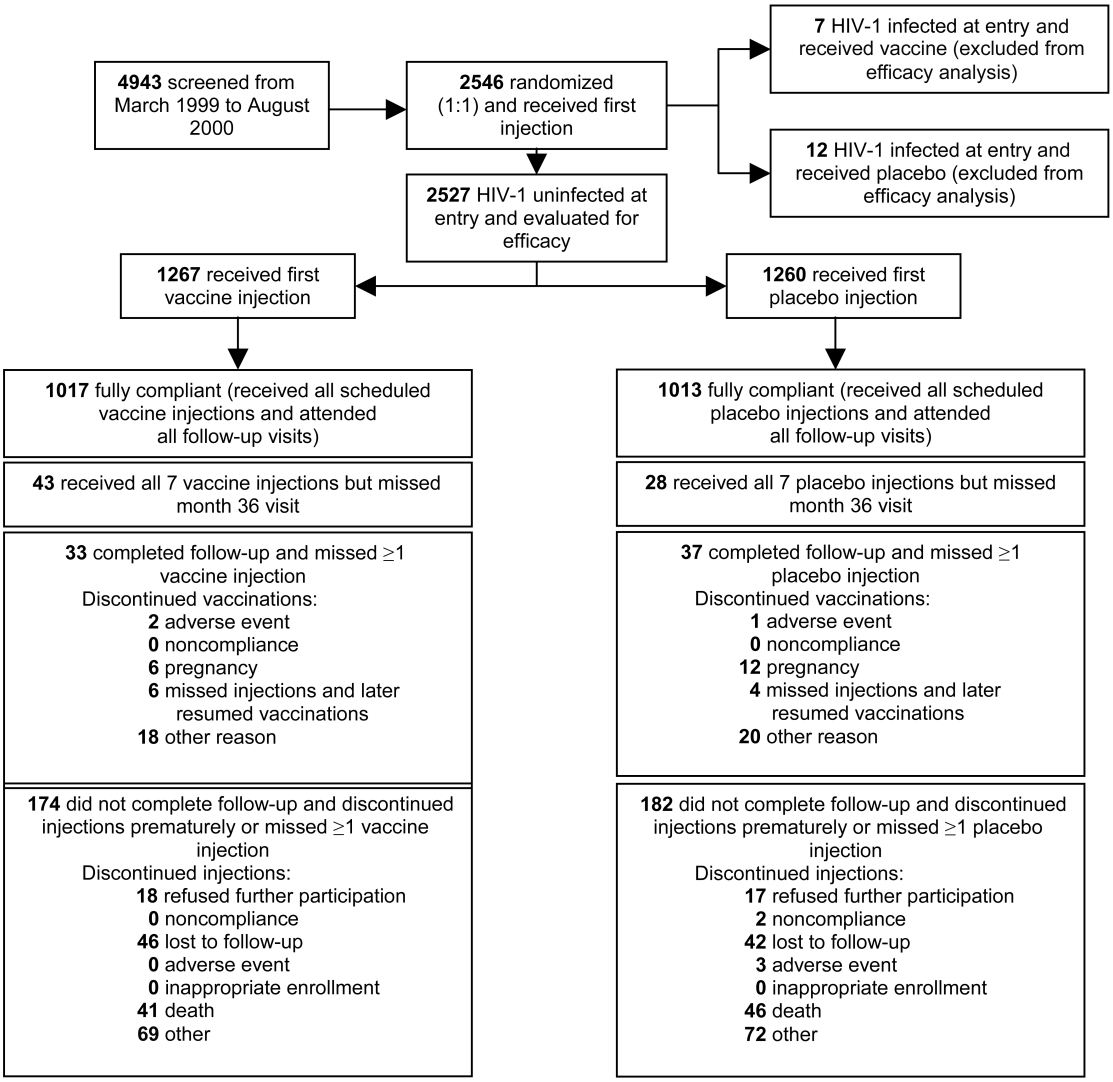

Figure 1. Flow of study participants

plasma by use of the ViroSeq Sample Preparation Kit (Applied Biosystems). Full-length gp120 sequences were amplified from samples by RT-PCR. The RT-PCRs were performed independently by use of commercially available kits (for RT, First Strand cDNA Synthesis Kit from Amersham Biosciences; for PCR, Sigma-Aldrich). All resulting PCR products were cloned into a bacterial plasmid (pCR 2.1-TOPO; Invitrogen) and sequenced by use of BigDye 3.1 reaction mix and an ABI-3100 automated DNA sequencer (Applied Biosystems). More than 200 full-length gp120 sequences were aligned by use of a proprietary software package (VaxGen) and subjected to phylogenetic analysis by use of Phylogenetic Analysis Using Parsimony software (Sinauer Associates). A complete description of the sequence methods and analyses will be presented elsewhere (Jobes et al., manuscript in preparation). All testing followed manufacturers' instructions.

Objectives and End Points

HIV-1 infection was the primary end point for vaccine efficacy; secondary end points were safety and delayed progression of HIV-1 disease. Disease progression was evaluated on the basis of clinical (initiation of antiretroviral therapy [ART] and onset of AIDS-defining conditions) and biological (CD4 cell count and plasma HIV-1 load) end points. Volunteers with incident HIV-1 infection received HIV care per Thailand national guidelines [23, 24]. Before October 2001, HIV-1–infected volunteers with a CD4 cell count <500 cells/mL were treated with 2 nu-

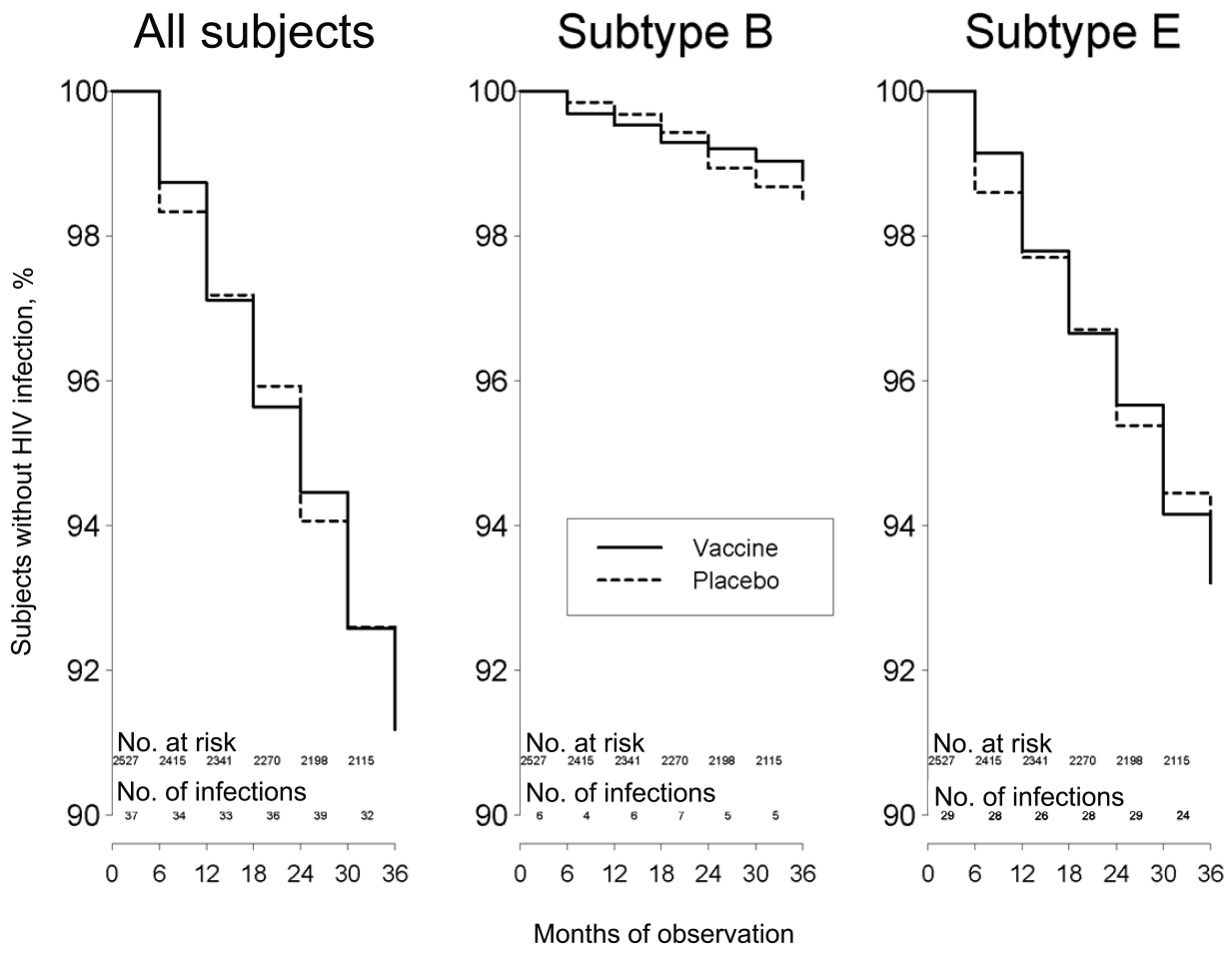

Figure 2. Kaplan-Meier curves for the time to the estimated date of HIV-1 infection during each 6-month interval for the intention-to-treat cohort, with all infections included regardless of whether the subtype was determined *(A);* 1 minus the cumulative incidence of infection with subtype B *(B);* and 1 minus the cumulative incidence of infection with subtype E *(C).*

cleoside reverse-transcriptase inhibitors. In October 2001, guidelines were revised to include highly active ART for those with a CD4 cell count <200 cells/mL.

Statistical Analysis

Sample size estimation. Vaccine efficacy was defined as (1 − relative risk of infection) × 100%. The trial design had 90% power to reject the null hypothesis with a demonstrated vaccine efficacy of 30% when the true vaccine efficacy was 67.5% ($P = .05$, 2-sided test). Power for the primary efficacy analysis of the intention-to-treat (ITT) cohort (having received at least 1 vaccination) was estimated on the basis of computer simulations, by use of a discrete failure-time model that assumed 2500 individuals enrolled, a 1:1 vaccine:placebo ratio, no vaccine effect until the third immunization and "full effect" thereafter, a placebo-arm infection rate of 4% per year, and losses to follow-up of 20%, 15%, and 10% in years 1, 2, and 3, respectively. Under these assumptions, 106 incident infections were expected in the placebo group, and 106, 82, and 50 incident infections were expected in the vaccine group if vaccine efficacy equaled 0%, 30%, and 67.5%, respectively. Statistical power was estimated by the proportion of 95% confidence intervals (CI) for vaccine efficacy not covering the null-hypothesis value. For the 1 interim analysis and the final efficacy analysis, significance levels for vaccine efficacy were $P = .027$ and $P = .0494$, respectively.

Primary end-point analysis. All participants were included in the safety analyses. Vaccine efficacy analyses included all participants in the ITT cohort. Kaplan-Meier curves were used to estimate the probability of being uninfected as a function of time from first vaccination. Log-rank tests were used to compare time-to-infection distributions between study arms. Cox proportional hazards models were used to estimate vaccine efficacy, with estimated infection times grouped into six 6-month periods. A simulation-based procedure was used to estimate the 95% CI for vaccine efficacy over time [25]. Adjusted

Table 1. Cumulative HIV-1 incidence among injection drug users (IDUs) participating in the AIDSVAX B/E vaccine trial, Bangkok, Thailand.

Category, parameter	Vaccine (n = 1267)		Placebo (n = 1260)		All (n = 2527)	
	No. infected/ total no.	Percentage (95% CI)	No. infected/ total no.	Percentage (95% CI)	No. infected/ total no.	Percentage (95% CI)
Sex						
Male	100/1191	8.4 (6.9–10.1)	101/1170	8.6 (7.1–10.4)	201/2361	8.5 (7.4–9.7)
Female	6/76	7.9 (3.0–16.4)	4/90	4.4 (1.2–11.0)	10/166	6.0 (2.9–10.8)
Age						
⩽25 years	56/601	9.3 (7.1–11.9)	50/633	7.9 (5.9–10.3)	106/1234	8.6 (7.1–10.3)
>25 years	50/666	7.5 (5.6–9.8)	55/627	8.8 (6.7–11.3)	105/1293	8.1 (6.7–9.7)
Education						
Less than primary	3/57	5.3 (1.1–14.6)	6/70	8.6 (3.2–17.7)	9/127	7.1 (3.3–13.0)
Primary	33/358	9.2 (6.4–12.7)	34/344	9.9 (6.9–13.5)	67/702	9.5 (7.5– 12.0)
Secondary	47/576	8.2 (6.1–10.7)	48/592	8.1 (6.0–10.6)	95/1168	8.1 (6.6–9.9)
Vocational/college	23/276	8.3 (5.4–12.2)	17/254	6.7 (3.9–10.5)	40/530	7.5 (5.4–10.1)
Behavioral risk[a]						
Lower	43/605	7.1 (5.2–9.5)	38/595	6.4 (4.6–8.7)	81/1200	6.8 (5.4–8.3)
Higher	63/662	9.5 (7.4–12.0)	67/665	10.1 (7.9–12.6)	130/1327	9.8 (8.2–11.5)

[a] Higher risk was defined as 2 or more of the following criteria being met at the baseline risk assessment: use of injection drugs regularly; use of injection drugs daily or weekly; use of injection drugs with shared needles; history of incarceration during the past 6 months; partner was an IDU; or sharing needles with partner. Lower risk was defined as the presence of <2 of these criteria.

vaccine efficacy was estimated by including demographic and baseline risk-behavior variables as covariates. Similar statistical methods were used to assess HIV-1 subtype E vaccine efficacy, with participants with non–subtype E infections censored at their estimated infection dates.

Secondary end-point analysis. Time-to-event analysis assessed the time between the date of HIV-1 infection and disease progression. Three outcomes were evaluated: treatment initiation; first treatment initiation or viral load >10,000 copies/mL starting at 1 month after infection, to avoid the acute stage; and the first AIDS-defining condition. Generalized estimation equations were used to model pretreatment HIV-1 load and CD4 cell count trajectories and estimated the difference in mean outcomes between the vaccine and placebo recipients.

Antibody response. Scatter plots were used to descriptively compare preinfection antibody response levels between HIV-1–infected and HIV-1–uninfected vaccine recipients; Wei-Johnson tests were used to evaluate differences between these groups at 1 or more time points. Case-cohort Cox proportional hazards models (adjusted for demographic and behavioral variables) were used to estimate the relative risks of HIV-1 infection for quartiles of antibody level included as time-dependent covariates [26]. Participants with outlying intervals between immunization and sampling (>50 days) were excluded. All P values were 2-sided and were unadjusted for multiplicity.

Ethics Considerations

The protocol of the present study was reviewed and approved by the ethics review committees of the Thailand MOPH, Mahidol University, and the BMA and by an institutional review board of the CDC. A data and safety monitoring board (DSMB) met every 6 months to review safety (e.g., reactogenicity, adverse events, and deaths) and to conduct the 1 interim efficacy analysis. At this analysis, the trial could have been stopped if statistically significant protection from HIV-1 infection was demonstrated among vaccine recipients. No specific futility analysis was planned.

RESULTS

Screening and enrollment. The screening, enrollment, and risk characteristics of the trial participants have been described elsewhere [27, 28]. Briefly, between March 1999 and August 2000, 4943 IDUs were screened, and 2546 were enrolled. Their median age was 26.0 years (range, 20–59 years); 93.4% were men, and 67.3% had at least a secondary education. During the 6 months before enrollment, 93.8% reported injecting, and 33.0% reported needle sharing; 61.3% reported having received methadone detoxification, 20.9% reported having received methadone maintenance, and 17.9% reported not having received drug treatment. Almost all volunteers had injected heroin (98.5%), and the remainder had injected stimulants or benzodiazepines. Daily injection was reported by 39.4%. Of the 446 (17.5%) who reported incarceration during the prior 6 months, 12.0% reported having injected in police holding cells, and 11.2% reported having injected in prisons.

Trial conduct. Of the 2546 IDUs enrolled, 2295 (90.1%) were followed up for 36 months or until HIV-1 seroconversion (figure 1). Of the enrolled volunteers, 230 were identified as

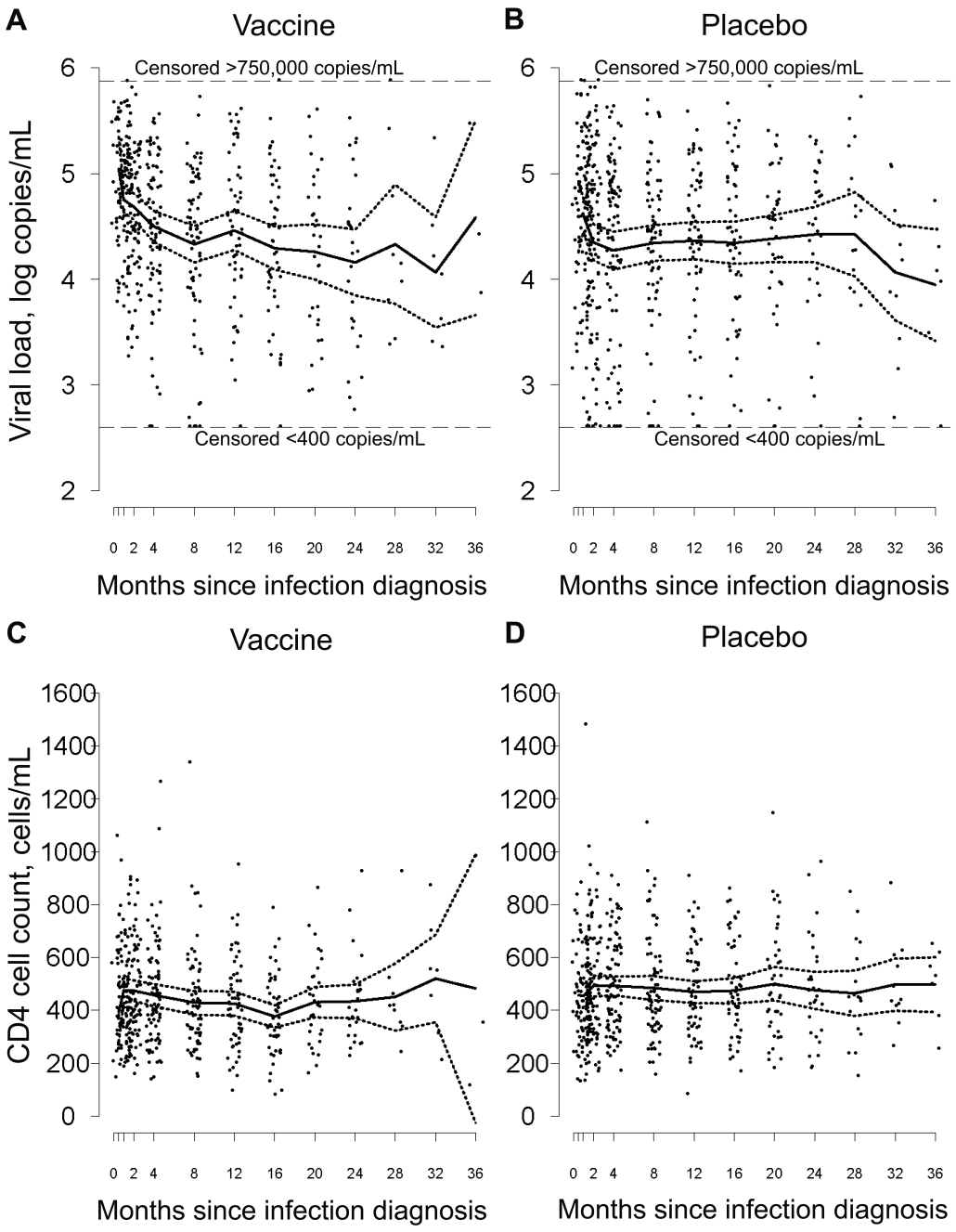

Figure 3. Pretreatment log plasma HIV-1 RNA loads over time in vaccine recipients *(A)* and placebo recipients *(B)* and pretreatment CD4 cell counts over time in vaccine recipients *(C)* and placebo recipients *(D),* for study participants in the intention-to-treat cohort who became infected with HIV-1. The solid lines indicate average values, and the dotted lines indicate 95% confidence intervals.

being HIV-1 infected. Of these, 79 started ART before October 2001, and 18 started after [23, 24, 29]. Later, immunobloting or NAT revealed that 19 enrolled participants were HIV-1 infected at screening. Thus, the ITT cohort consisted of 2527 HIV-1–negative volunteers at entry: 1267 in the vaccine group, and 1260 in the placebo group. The DSMB interim safety and efficacy analysis in October 2002 recommended that the trial proceed as planned.

During the trial, self-reports of drug injection decreased from 93.8% to 56.0% ($P < .001$), and self-reports of needle sharing decreased from 33.0% to 16.3% ($P < .001$) [27]. No drug-use urine testing to validate the self-reports was conducted. Thirty-nine trial-related social harms, including discrimination and loss of opportunity, were reported by 37 volunteers [13]. Disturbance in a personal relationship related to the voluntary disclosure of trial participation was the most common event (33 volunteers).

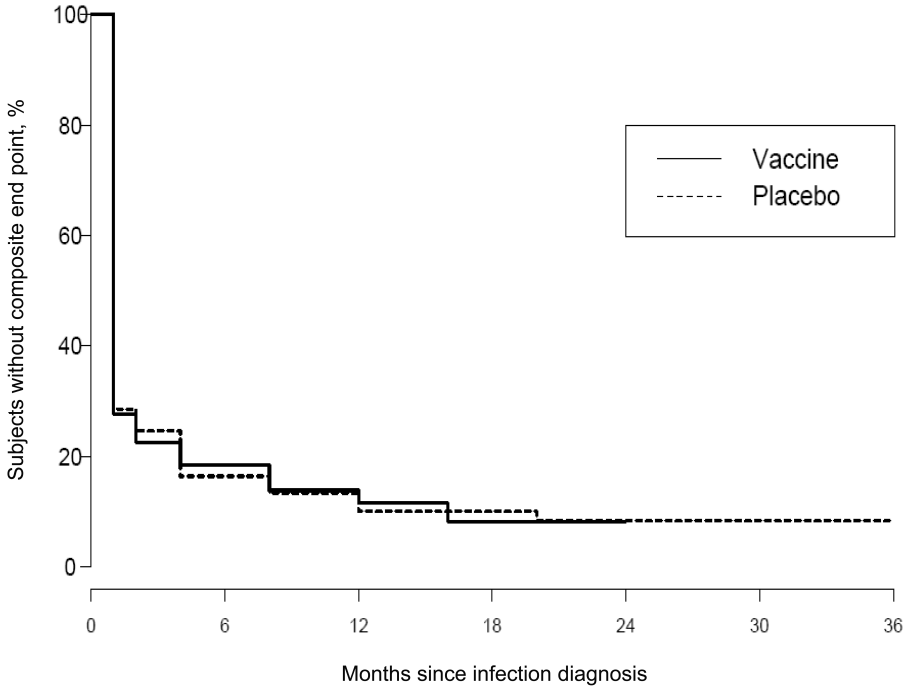

Figure 4. Kaplan-Meier curves for the time from infection diagnosis to the composite end point of drug-treatment initiation or viral failure (>10,000 copies/mL), for study participants in the intention-to-treat cohort who became infected with HIV-1.

Social harms were typically resolved with counseling by trial staff. Police harassment or arrests in relation to trial participation were not among the social harms reported [13].

Safety. Tenderness at the injection site—in 902 (71.0%) vaccine recipients and 830 (65.7%) placebo recipients—was the most commonly reported adverse event and did not increase with multiple injections. Of 414 serious adverse events reported, accidental injury was the most common (128 [30.9%]), followed by drug overdose (49 [11.8%]), and sepsis (22 [5.3%]). The most common cause of 102 deaths was drug overdose (38 [37.3%]), sepsis (17 [16.7%]), accidental injury (12 [11.8%]), and suicide (8 [7.8%]); homicide as a cause of death was not reported. There were no differences between vaccine and placebo recipients in these respects.

Rates of infection and vaccine efficacy. The pooled HIV-1 incidence rate was 3.4 infections/100 person-years (95% CI, 3.0–3.9 infections/100 person-years). There were 106 HIV-1 infections (8.4%) in the vaccine group and 105 (8.3%) in the placebo group. Of the 211 HIV-1 infections, 164 (77.7%; 83 in vaccine recipients, and 81 in placebo recipients) were subtype CRF01_AE; 32 (15.2%; 14 in vaccine recipients, and 18 in placebo recipients) were subtype B′, 1 was subtype B (in a vaccine recipient), and the remaining 14 (6.6%) were untypeable. The covariate-unadjusted estimate of vaccine efficacy was 0.1% (95% CI, −30.8 to 23.8; $P = .99$, log-rank test). The estimate of the unadjusted vaccine efficacy for subtype CRF01_AE infection was −1.4% (95% CI, −37.7 to 25.4; $P = .93$, log-rank test). Estimated curves for remaining free of HIV-1 infection by subtype and study arm are shown in figure 2.

There was no evidence of a calendar-time trend in incidence by 6-month time period. HIV-1 infection rates by study arm, sex, age, education, and baseline risk behavior are shown in table 1. The unadjusted and adjusted estimates of vaccine efficacy were similar, suggesting no confounding by an imbalance of demographic factors or risk behaviors at baseline.

Markers of HIV-1 disease progression. HIV-1–infected participants were followed for a maximum of 36 months (median, 22 months). No significant differences between HIV-1–infected vaccine recipients and HIV–1–infected placebo recipients were found with regard to plasma HIV-1 loads or CD4 cell counts (figure 3), onset or clinical course of AIDS-defining conditions, time to treatment initiation, and time to the first event of viral failure or treatment initiation (figure 4). This analysis was practically equivalent to assessing time to viral failure without "confounding" by treatment, because of the 183 events, only 3 were due to treatment initiation before viral failure. These results were similar when stratified by subtype B and subtype E infection.

Antibody response. The peak preinfection antibody levels for gp120, A244 V2, A244 V3, blocking of A244 binding to CD4, and MN neutralization were not significantly different between the 106 HIV-1–infected and the 115 randomly sampled

uninfected vaccine recipients ($P > .2$). Among vaccine recipients, with or without adjustment for age, education, and behavioral risk, the level of the most recent peak preinfection immune responses did not correlate with the rate of HIV-1 infection ($P > .2$). In the samples assessed for antibody response, all vaccine recipients, but none of the 12 placebo recipients, developed antibodies to gp120. Figure 5 shows all peak antibody levels for uninfected vaccine recipients and for vaccine recipients with incident HIV-1 infection measured before the estimated date of HIV-1 infection. The geometric mean peak preinfection neutralization titers in vaccine recipients at months 1.5, 6.5, 12.5, 18.5, 24.5, and 30.5 were 214, 3972, 5707, 5327, 4482, and 4247, respectively.

DISCUSSION

In this successfully completed trial of AIDSVAX B/E, the candidate vaccine did not prevent HIV-1 infection or delay disease progression. No evidence was found of vaccine efficacy against either subtype B or E virus in predefined demographic or risk-behavior subgroups with the highest levels of antibody response to the vaccine.

The lack of vaccine efficacy in this study is similar to that in a recent trial of a similar vaccine, rgp120 B/B, which was evaluated among men who have sex with men and women at high risk in North America and The Netherlands [22, 30]. Unlike in the present trial, in the rgp120 B/B trial there was an interesting trend toward modest efficacy, although it was not significant after adjustment for multiplicity in nonwhite persons and in volunteers with the highest HIV risk behavior. Possible explanations for any disparity between the 2 trials include differences in demographics, circulating HIV subtypes, and route of transmission (sexual vs. parenteral). However, demographic differences do not seem to play a role, because, in the rgp120 B/B trial, the few Asian participants did not contradict the trend in nonwhite persons. Differences in HIV subtypes is also an unlikely explanation, because, in the Thai

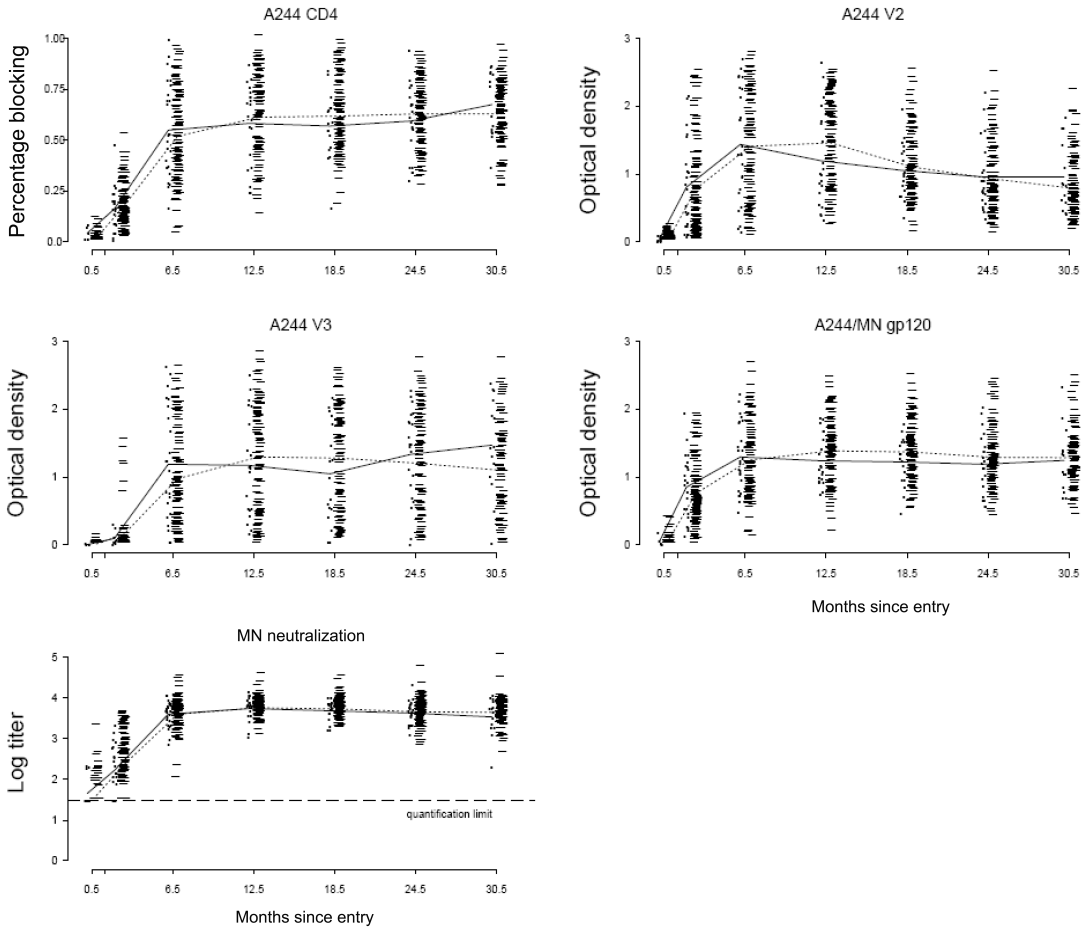

Figure 5. Average antibody levels for vaccine recipients with incident HIV-1 infection *(solid lines)* and for uninfected vaccine recipients *(dotted lines),* for study participants in the intention-to-treat cohort. For vaccine recipients with incident HIV-1 infection, antibody levels were measured in the last peak sample collected before the estimated date of HIV-1 infection; for uninfected vaccine recipients, antibody levels were measured for all 7 peak time points (at months 0.5, 1.5, 6.5, 12.5, 18.5, 24.5, and 30.5).

trial, the genetic variation between the infecting subtype CRF01_AE viruses and the vaccine subtype E components was less than that between the infecting subtype B viruses and the subtype B vaccine components (D. Jobs, personal communication). Thus, any differences in outcome between the 2 trials, if real, are likely the result of dissimilarities between sexual and parenteral HIV transmission with respect to dynamics, viral loads, and local and systemic protective mechanisms.

It has been hypothesized that the failure in both trials was due to the lack of induction of neutralizing antibodies against genetically diverse primary HIV-1 isolates. However, there are a number of important findings. The vaccines in both trials appeared to be safe, and earlier concerns about possible enhancement of HIV-1 disease progression [31–33] could not be confirmed. In the rgp120 B/B trial, higher peak antibody responses to the vaccine appeared to correlate with a lower risk of HIV-1 infection [34]. Of note, the AIDSVAX B/E vaccine is being used as the booster portion of a combination regimen that uses an attenuated canarypox vector (ALVAC vCP1521; Aventis Pasture) in the world's third phase 3 HIV-1 vaccine efficacy trial, which is currently under way in Thailand [35].

Despite the lack of efficacy of AIDSVAX B/E as a stand-alone vaccine, a treasure of useful information has been obtained from this trial and from the preceding 5 years of epidemiological, biomedical, and sociobehavioral research among IDUs in Bangkok [27, 28]. Measures of HIV incidence and their changes over time are perhaps the best documented for any population group in the world [10, 36–39], and studies of viral characterization [1, 18, 19, 40, 41] and disease progression [42–44] have provided crucial information for current and future HIV vaccine trials. Our study has demonstrated that IDUs can be enrolled and followed and are compliant and that counseling can quickly, although not completely, lower risk behaviors and sustain this level over time [27, 28]. The trial also demonstrated the importance of monitoring drug-use trends so that drug-use counseling can be effectively tailored [45].

No clean injection equipment was made available to participants at study clinics, and some have identified this as an ethics problem. However, Thailand's narcotics law prohibits the distribution of clean injection equipment, and its HIV-prevention policy favors cessation of heroin use through methadone treatment over the provision of clean equipment. Nevertheless, clean needles and syringes can be bought at drug and convenience stories without prescription for the modest price of 4–10 Thai bahts (US $0.10–$0.20). Indeed, when asked at every 6-month study visit (as part of our risk assessment), >95% of participants said they could obtain new and unused needles without any problem. Moreover, the inclusion of needle exchange as a measure to prevent HIV infection, which would not have been feasible outside the clinical trial setting, would have seriously affected the external validity of our phase 3 efficacy study.

Toward the end of the trial, in February 2003, the Thai Government initiated its "war on drugs," to reverse the increasing trend in methamphetamine use that had begun during the mid 1990s [46, 47]. Heroin users in drug treatment, the population from which we recruited our participants, were not the campaign target [46]. Consequently, police harassment and arrest in relation to trial participation were not among the social harms reported [13]. Several human-rights organizations have expressed concern [48] over the reported increase in drug-use-related homicides during the war on drugs; however, homicide was not among the causes of death reported in our trial.

An effective vaccine remains the best hope to control the global HIV-1 epidemic, especially in developing countries. It is disappointing that the first 2 HIV-1 candidate vaccines did not prevent infection. Nonetheless, the tremendous amount of scientific information gained from the years of work leading up to, as well as during, the conduct of these studies will be invaluable in preparing for future large-scale HIV-1 vaccine trials—as well as other biomedical intervention trials in high-risk populations around the world [49].

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VaxGen, Inc. Phillip Berman, Lisa Brooks, Marlene Chernow, Don Francis, Carolyn Gee, Marc Gurwith, William Heyward, Tina Ippolito, David Jobes, Tina Kalanon, Elizabeth Li, Aimee Luck, Karin Orelind, Patti Orozco-Cronin, Michael L. Peterson, and Faruk Sinangil.

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Acknowledgments

We thank Piyamaith Yodnane, Suwanee Raktham, Krit Hiranras, Soonthorn Srichan, Veerawat Hantavichai, Paichit Pawabutr, Prayura Kunasol, Sornchai Looareesuwan, Pornchai Matangkasomabut, Praphan Kitisin, Nathan Winslow, Mark McLaughlin, Marc Drucker, Jim Young, Kate MacQueen, Alan Greenberg, and Charles Vitek.

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