ORIGINAL ARTICLE

Efficacy Trial of a DNA/rAd5 HIV-1 Preventive Vaccine

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ABSTRACT

BACKGROUND

A safe and effective vaccine for the prevention of human immunodeficiency virus type 1 (HIV-1) infection is a global priority. We tested the efficacy of a DNA prime–recombinant adenovirus type 5 boost (DNA/rAd5) vaccine regimen in persons at increased risk for HIV-1 infection in the United States.

METHODS

At 21 sites, we randomly assigned 2504 men or transgender women who have sex with men to receive the DNA/rAd5 vaccine (1253 participants) or placebo (1251 participants). We assessed HIV-1 acquisition from week 28 through month 24 (termed week 28+ infection), viral-load set point (mean plasma HIV-1 RNA level 10 to 20 weeks after diagnosis), and safety. The 6-plasmid DNA vaccine (expressing clade B Gag, Pol, and Nef and Env proteins from clades A, B, and C) was administered at weeks 0, 4, and 8. The rAd5 vector boost (expressing clade B Gag-Pol fusion protein and Env glycoproteins from clades A, B, and C) was administered at week 24.

RESULTS

In April 2013, the data and safety monitoring board recommended halting vaccinations for lack of efficacy. The primary analysis showed that week 28+ infection had been diagnosed in 27 participants in the vaccine group and 21 in the placebo group (vaccine efficacy, –25.0%; 95% confidence interval, –121.2 to 29.3; P=0.44), with mean viral-load set points of 4.46 and 4.47 HIV-1 RNA $\log_{10}$ copies per milliliter, respectively. Analysis of all infections during the study period (41 in the vaccine group and 31 in the placebo group) also showed lack of vaccine efficacy (P=0.28). The vaccine regimen had an acceptable side-effect profile.

CONCLUSIONS

The DNA/rAd5 vaccine regimen did not reduce either the rate of HIV-1 acquisition or the viral-load set point in the population studied. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT00865566.)

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The epidemic infection caused by the human immunodeficiency virus type 1 (HIV-1) is now in its fourth decade, with an estimated 2.5 million new infections occurring annually worldwide.[1] The number of newly infected persons, although diminishing, outpaces the number of patients who initiate antiretroviral therapy. Despite a number of successful prevention interventions that have been reported, including preexposure prophylaxis and treatment as prevention,[2-9] ultimate control of the HIV epidemic will most likely come only with the development of a safe and effective preventive vaccine.

This goal has proved to be elusive. Of the efficacy trials of HIV vaccines that have been reported thus far,[10-15] only one[15] has shown a modest relative reduction of 31% in HIV infections in a general Thai population. The Dale and Betty Bumpers Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases was established with a charge to facilitate the development of an HIV vaccine. The lead candidate was designed to elicit HIV-specific, multifunctional responses in CD4+ and CD8+ T cells and antibodies to envelopes of the major circulating strains. The resultant multigene, multiclade DNA prime–recombinant adenovirus type 5 vector boost (DNA/rAd5) vaccine underwent extensive preclinical and early-phase clinical testing and was found to be safe and immunogenic.[16-24] The HIV Vaccine Trials Network (HVTN) conducted a phase 2b efficacy trial of this vaccine regimen in at-risk populations in the United States.

Methods

Design and Study Population

This study, called HVTN 505, was a randomized, double-blind, placebo-controlled trial of the VRC's DNA/rAd5 HIV-1 vaccine. To be eligible for the study, men and transgender women between the ages of 18 and 50 years were required to be fully circumcised, to have a history of unprotected anal intercourse with one or more male or male-to-female transgender partners or anal intercourse with two or more male or male-to-female transgender partners in the 6 months before randomization, to have negative results on serum HIV-1 and HIV-2 antibody testing, to have an adenovirus serotype 5 (Ad5) serum neutralizing antibody titer of less than 1:18, and to have an alanine aminotransferase level of no more than 2.5 times the upper limit of the normal range. Participants were enrolled at 21 sites in the United States and provided written informed consent.

The original efficacy objective of the study was to evaluate the regimen's effect on viral load in 1350 participants. During the course of the study, the protocol was amended to raise the sample size to 2500 to provide sufficient statistical power to assess efficacy in the prevention of HIV-1 acquisition and to account for the use of preexposure prophylaxis.[7,15,16]

Study End Points

The primary efficacy end points were HIV infections diagnosed after week 28 (day 196) following enrollment through the 24-month study visit (termed week 28+ infection, which permitted time for receipt of the full immunization series and elicitation of an immune response) and the HIV-1 viral-load set point, which was defined as the mean plasma HIV-1 RNA level obtained 10 to 20 weeks after the diagnosis of HIV-1 infection and before the initiation of antiretroviral therapy. Primary safety end points were local and systemic reactogenicity and adverse events.

Secondary objectives included evaluation of all infections from enrollment through the 24-month visit in participants who were HIV-uninfected at enrollment (the modified intention-to-treat cohort) and evaluation of vaccine-induced immune responses. Exploratory objectives included the evaluation of risk behaviors and the use of antiretroviral drugs as prophylaxis before and after exposure.

Study Oversight

The study was approved by the institutional review board at the Fred Hutchinson Cancer Research Center, which served as a central institutional review board for 11 sites through agreements with these institutions. At the remaining 10 sites, the study was approved by the local institutional review board. All authors attest to the fidelity of the report to the protocol, which is available with the full text of this article at NEJM.org.

Vaccine Regimen and Administration

The DNA prime consisted of six closed circular plasmids (in a 1:1:1:1:1:1 ratio) designed to individually express HIV-1 clade B Gag, Pol, and Nef

and Env proteins from clades A, B, and C.[17,18] The DNA vaccine was administered in a 4-mg dose intramuscularly in the deltoid by means of Biojector at enrollment (week 0), week 4, and week 8. The DNA placebo was phosphate-buffered saline. The rAd5 boost consisted of four rAd5 vectors (in a 3:1:1:1 ratio) expressing an HIV-1 clade B Gag-Pol fusion protein and Env glycoproteins from clades A, B, and C.[19] The dose of 10^{10} particle units was administered intramuscularly in the deltoid by means of needle and syringe at week 24. The rAd5 placebo was the vector-free diluent.

SCREENING, RANDOMIZATION, AND ENROLLMENT

During the 56-day screening period, we obtained a medical history, performed a physical examination (including reporting of circumcision status), performed HIV and Ad5 serologic analyses, and measured serum alanine aminotransferase levels. We provided education concerning HIV vaccines, HIV testing, and risk reduction and reviewed alternatives to participation in this study. Eligible participants underwent randomization, with enrollment defined as receipt of the first dose of vaccine.

STUDY EVALUATIONS

Study visits were scheduled at months 0, 1, 2, 2.5, 6, 7, and 9 and then every 3 months through 24 months. A medical-history update, symptom-directed physical examination, and risk-reduction counseling (including the provision of free condoms), a social impact assessment, concomitant medications, HIV testing, and a questionnaire on behavioral risk and the use of prophylactic antiretroviral agents were performed at regular intervals. Screening for sexually transmitted infections occurred every 6 months.

HIV-INFECTED PARTICIPANTS

Participants with confirmed HIV-1 infection were asked to come to the study site for counseling, education, and referral to care. Follow-up within this study continued, and plasma HIV-1 RNA levels that were measured at 10, 12, 14, 16, and 20 weeks after diagnosis were averaged to determine the mean viral-load set point.

IMMUNOGENICITY ASSAYS

We used validated, described methods to assess vaccine-induced HIV-1–specific CD4+ and CD8+ T cells,[25] serum HIV-1–specific binding antibodies,[26-28] and neutralizing antibodies[29] 4 weeks after the administration of the rAd5 vaccine in a randomly selected pilot sample of 40 vaccine recipients (with data missing for T-cell studies in 1 recipient) and 10 placebo recipients who remained HIV-uninfected at 24 months. (For details, see Sections 2.1, 2.2, and 2.3 in the Supplementary Appendix, available at NEJM.org.)

STATISTICAL ANALYSIS

Participants underwent block randomization according to site with the use of computer-generated random numbers provided by the Statistical Center for HIV/AIDS Research and Prevention (SCHARP). We measured vaccine efficacy as 1 minus the hazard ratio for a diagnosis of HIV-1 infection after week 28 (day 196) following enrollment through the 24-month study visit and reported as a percentage. Vaccine efficacy was estimated with the use of a Cox proportional-hazards model with event time being the number of days from day 196 until the diagnosis of infection. Data for participants in whom infection was not diagnosed by the 24-month visit were censored at the time of the last test showing HIV-1 negativity. We used the log-rank test to assess whether vaccine efficacy differed from 0% and Kaplan–Meier plots to display the cumulative incidences of HIV-1 infection over time. The vaccine efficacy for preventing infection in the modified intention-to-treat population was analyzed similarly on the basis of the time from randomization.

We assessed the vaccine effect on the viral-load set point in participants with week 28+ infection by estimating the mean set points in the two study groups with a robust likelihood-based method.[30] This method accounts for missing viral-load values by means of linear model-based imputation (see Section 1.7 in the Supplementary Appendix).

The sample size of 2500 participants provided a power of 80% to detect a vaccine efficacy of 50% and a power of 84% or more to detect a mean difference of 1.0 $\log_{10}$ copies per milliliter in the viral-load set point if the vaccine efficacy were 50% or less.

We planned two interim analyses for efficacy futility to occur once the 30th and 48th participant with week 28+ infection had the study visit 20 weeks after diagnosis. The prespecified guide-

line for efficacy futility was that both the 95% confidence intervals for vaccine efficacy and the difference in viral load were below their respective design alternatives of reductions of 50% and 1.0 $\log_{10}$ copies per milliliter, respectively. These criteria were met at the time of the data freeze (March 22, 2013) for the April 22, 2013, review by the data and safety monitoring board (upper confidence limits, 29% for vaccine efficacy and 0.95 for the difference in viral load). This milestone triggered the recommendation to halt vaccinations. Site personnel were immediately notified and administered no further vaccinations; participants were informed and were made aware of their study-group assignment. The data presented are complete through April 22, 2013. All P values are two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

PARTICIPANT ACCRUAL, ENROLLMENT, AND DISPOSITION

From June 11, 2009, to March 27, 2013, a total of 2504 participants were enrolled (Fig. 1). Of these participants, 8 were retrospectively determined to have been HIV-infected at enrollment. Thus, in the modified intention-to-treat population, 2496 participants underwent randomization to receive vaccine (1251 participants) or placebo (1245 participants). The yearly rate of loss to follow-up was 4.8% (95% confidence interval [CI], 3.8 to 6.1) in the vaccine group and 6.6% (95% CI, 5.4 to 8.0) in the placebo group (P=0.05) (Fig. S1 in the Supplementary Appendix).

BASELINE CHARACTERISTICS

In the modified intention-to-treat population, 98% of the participants were men, with a median age of 29; 70% were white, 16% black, 8% Hispanic, and 1% Asian, with the remaining 5% listed as "other." Overall, baseline characteristics were well balanced in the two study groups (Table S1 in the Supplementary Appendix).

The study population was at substantial risk for HIV-1 infection, with 29% reporting three to four male sexual partners and 26% reporting five or more male partners in the 3 months before enrollment; 18% reported having sexual activity with a known HIV-positive male partner. Unprotected insertive anal sex was reported by 55% and unprotected receptive anal sex by 46%.

PRIMARY EFFICACY ANALYSES

The primary analysis cohort consisted of participants who were HIV-negative at 196 days after enrollment and therefore at risk for week 28+ infection (967 in the vaccine group and 947 in the placebo group). Of these participants, 95% of vaccine recipients and 97% of placebo recipients received all four vaccinations.

Week 28+ infection was diagnosed in 27 participants in the vaccine group and 21 in the placebo group, yielding annual incidences of 2.8% (95% CI, 1.9 to 4.1) and 2.3% (95% CI, 1.4 to 3.5), respectively; the estimated vaccine efficacy was −25.0% (95% CI, −121.2 to 29.3; P=0.44) (Table 1 and Fig. 2A). The estimated vaccine efficacy in the per-protocol cohort was −45.3% (95% uncertainty interval, −145.9 to 88.5; P=0.34) (Section 1.6.4 and Fig. S8 in the Supplementary Appendix). From enrollment through 28 weeks, a total of 24 infections occurred (14 in the vaccine group and 10 in the placebo group), yielding a total of 72 HIV infections from enrollment through the 24-month visit (41 in the vaccine group and 31 in the placebo group). In the modified intention-to-treat population, the yearly HIV incidence was 2.7% (95% CI, 1.9 to 3.6) in the vaccine group and 2.1% (95% CI, 1.4 to 2.9) in the placebo group (P=0.28) (Fig. 2B).

Of the 48 participants with week 28+ infection, 47 were included in the analysis of the viral-load set point. One placebo recipient in whom antiretroviral therapy was initiated before infection was diagnosed was excluded from this analysis. The estimated mean HIV-1 RNA viral-load set points in the vaccine and placebo groups were 4.46 and 4.47 $\log_{10}$ copies per milliliter, respectively, for an overall difference (placebo minus vaccine) of 0.002 copies per milliliter (95% CI, −0.55 to 0.68; P=0.99) (Table 1 and Fig. 3A). In the modified intention-to-treat population, the estimated mean viral-load set points in the vaccine and placebo groups were 4.51 and 4.54 $\log_{10}$ copies per milliliter, respectively (Fig. 3B, and Section 1.8.1 and Table S8 in the Supplementary Appendix).

ANTIRETROVIRAL PROPHYLAXIS

We assessed the use of antiretroviral agents for prevention by means of case-report forms obtained during the study and by an audio computer-assisted self-administered interview (ACASI)

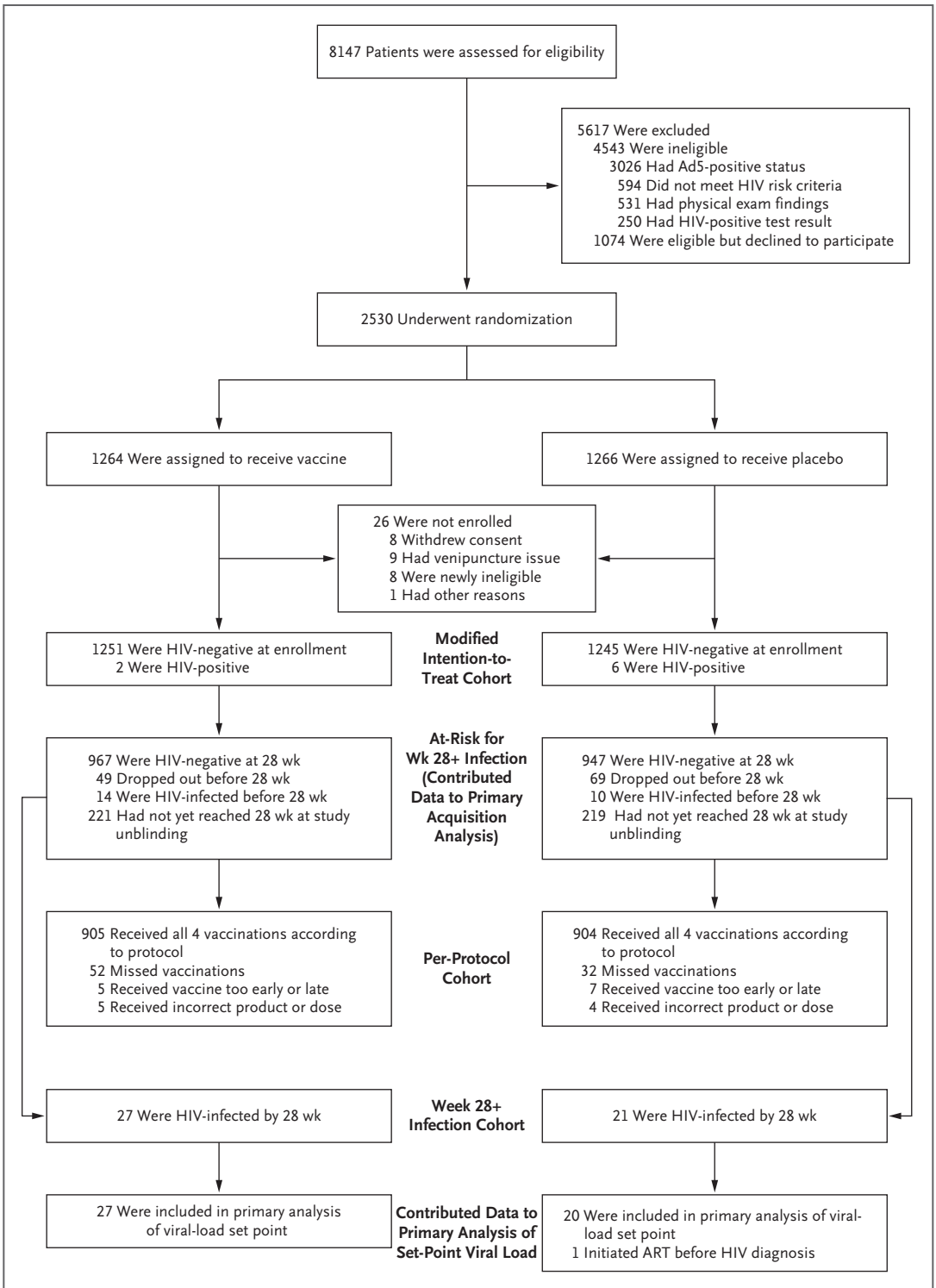

Figure 1. Enrollment and Outcomes.

Participants could have more than one reason for ineligibility; only the four most common reasons are listed. Participants who were not included in the per-protocol cohort for multiple reasons are listed in the category in which the first protocol violation was reported.

Table 1. Rate of Week 28+ HIV-1 Infection, Vaccine Efficacy, Mean Viral-Load Set Point, and Difference in Viral Load (Modified Intention-to-Treat Population).*

Variable	Vaccine (N=1251)				
	No. Evaluated	No. with Infection	No. of Person-Years	Rate	Mean HIV-1 RNA Viral-Load Set Point
				no./person-yr	*log_{10} copies/ml*
All participants	1251	27	1539.3	0.018	4.46
Race or ethnic group§					
Nonwhite or Hispanic	389	12	480.3	0.025	4.06
Non-Hispanic white	862	15	1059.1	0.014	4.90
Risk score¶					
Low	454	5	566.8	0.009	4.96
Low to medium	337	5	397.6	0.013	4.58
Medium to high	208	4	267.9	0.015	2.87
High	252	13	307.1	0.042	4.41
Body-mass index‖					
≤25.34	619	15	750.1	0.02	4.59
>25.34	631	12	787.2	0.015	4.20

* Results are based on all data entered into the database before the date of unblinding (April 23, 2013), with the exception of viral-load data, which are included if they were received by July 22, 2013.
† Vaccine efficacy was measured as 1 minus the hazard ratio for a diagnosis of HIV-1 infection after week 28 (day 196) following enrollment through the 24-month study visit; this value is reported as a percentage. Vaccine efficacy was estimated with the use of a Cox proportional-hazards model.
‡ The difference in viral load, which was measured as the mean viral-load set point in the placebo group minus that in the vaccine group, was estimated with the use of the method of Little and An.[30]
§ Race or ethnic group was self-reported.
¶ The risk score is a function of two risk-behavior variables collected at enrollment by means of a questionnaire: an indicator that the number of male sexual partners was greater than three and an indicator of unprotected receptive anal sexual activity during the past 3 months.
‖ The body-mass index is the weight in kilograms divided by the square of the height in meters.

questionnaire, which was implemented after the release of the results of the Preexposure Prophylaxis Initiative (iPrEx) study.[7] Preexposure prophylaxis was reported by 13 participants (1.0%) in each study group, and postexposure prophylaxis was reported by 41 participants (3.3%) in each group.

BEHAVIORAL RISK

An analysis of baseline data with respect to behavioral risk obtained from ACASI questionnaires identified two variables that predicted the risk of HIV-1 infection: a history of more than three male sexual partners or unprotected receptive anal sex in the 3 months before enrollment. The behavioral risk score, a weighted average of these two variables (Section 1.3 in the Supplementary Appendix), was highly predictive of the risk of HIV-1 infection, with a hazard ratio of 6.01 (95% CI, 3.15 to 11.48) for participants with both risk factors, as compared with those with neither risk factor (P<0.001).

The frequency of these two risk behaviors remained at or below baseline levels throughout the study, with no significant between-group differences (Fig. S2 through S5 in the Supplementary Appendix).

SAFETY

The vaccine regimen had an acceptable side-effect profile. Vaccine recipients had a significantly higher rate of reactogenicity than did placebo recipients, but most reactions were mild or moderate (Section 1.4 and Table S2 in the Supplementary Appendix). Nonfatal adverse events were balanced in the two study groups, with only one

	Placebo (N=1245)				Vaccine Efficacy†	Difference in Viral Load‡
No. Evaluated	No. with Infection	No. of Person-Years	Rate	Mean HIV-1 RNA Viral-Load Set Point		
			no./person-yr	*log_{10} copies/ml*	*% (95% CI)*	*value (95% CI)*
1245	21	1508.5	0.014	4.47	–25.0 (–121.2 to 29.3)	0.00 (–0.55 to 0.68)
369	7	472.6	0.015	4.52	–70.9 (–334.1 to 32.7)	0.45 (–0.21 to 1.42)
876	14	1035.9	0.014	4.43	–3.0 (–113.4 to 50.3)	–0.47 (–1.10 to 0.62)
465	3	574.3	0.005	4.46	–69.2 (–607.9 to 59.6)	–0.50 (–1.31 to 0.14)
313	6	371.2	0.016	4.29	23.0 (–152.4 to 76.5)	–0.29 (–1.30 to 0.92)
209	6	254.4	0.024	4.68	37.7 (–120.6 to 82.4)	1.80 (–0.67 to 3.04)
258	6	308.6	0.019	4.59	–114.4 (–464.0 to 18.5)	0.18 (–1.18 to 1.39)
629	16	741.0	0.022	4.37	8.7 (–84.7 to 54.9)	–0.22 (–0.98 to 0.58)
615	5	765.6	0.007	5.62	–133.2 (–561.9 to 17.9)	1.42 (0.46 to 2.58)

event (a severe viral syndrome) judged to be related to a study product. Six participants (all in the placebo group) died during the study (Section 1.4.2 in the Supplementary Appendix).

IMMUNOGENICITY

Vaccine-induced, HIV-specific response rates in CD4+ T cells (61.5%) and CD8+ T cells (64.1%) were detected ex vivo by intracellular cytokine staining (Fig. S14 in the Supplementary Appendix). The median frequency of expression of interferon-γ, interleukin-2, or both by CD4+ T cells was 0.1%; these cells predominantly targeted Gag (48.7%) and Env (38.5%) antigens. By contrast, the median frequency of total cytokine-expressing CD8+ T cells was 0.2%, with predominant recognition of Env (56.4%).

The vaccine induced a rate of IgG response of 100% to the vaccine strain envelopes (VRC clades A, B, and C), to the group M consensus envelope (ConS glycoprotein [gp]140), and to gp41 but a rate of only 48% to the gp120 antigen (Fig. S15 and S16 in the Supplementary Appendix). IgG response rates to V1-V2 Env were low as measured either to the gp70 V1-V2 (case A2) antigen from the correlates analysis in the RV144 trial[27] (18%) or to the matched VRC clade A gp70 V1-V2 (VRC clade A) antigen (20%). Serum Env IgA response rates and magnitudes were lower than those for IgG. Serum IgA responses to A1.Con gp140 (a clade A envelope protein), a positive correlate of infection risk in the RV144 trial,[27,31] were 43% (Fig. S15 in the Supplementary Appendix). Response rates for neutralizing antibodies were low (2.5 to 27.5%) and when present were only against tier 1 isolates, which can be more easily neutralized in vitro[32] (Fig. S17 in the Supplementary Appendix).

DISCUSSION

Thirty years after the discovery of HIV, a safe and effective vaccine is still not in sight. Of the six efficacy trials that have been conducted to date (including this study), only one, the RV144 Thai trial of ALVAC/gp120, showed protective efficacy.[15] Two trials of recombinant bivalent gp120 showed no benefit, and the Step study (HVTN 502) of another Ad5 vector vaccine expressing the internal proteins Gag, Pol, and Nef showed not only futility but an increased early risk of HIV acquisition in men who were uncircumcised or Ad5-seropositive at baseline.[33] In the Phambili study of the same vaccine, investigators in South

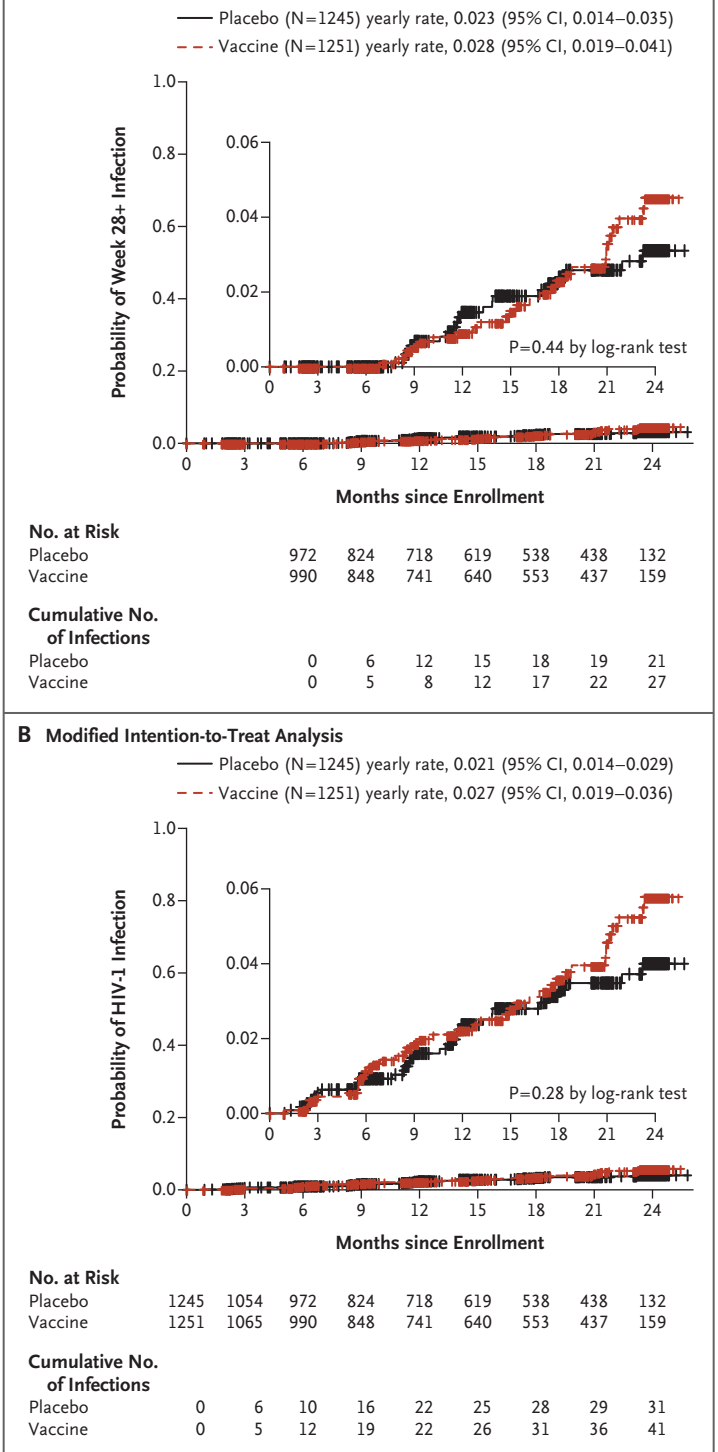

Figure 2. Cumulative Incidence of HIV-1 Infection in Two Population Subgroups.

Shown are the cumulative incidences of HIV-1 infection diagnosed from week 28 through month 24 (week 28+ infection) (Panel A) and HIV-1 infection in the modified intention-to-treat population (Panel B). Insets show the same data on an expanded y axis.

Africa discontinued the trial before full enrollment on the basis of the results of the Step study but recently reported a possible increase in HIV infections among vaccine recipients. However, because of early unblinding, this assessment is potentially confounded.[34]

In our study, we enrolled 2504 participants at 21 sites in the United States. On April 22, 2013, the data and safety monitoring board recommended stopping vaccinations. At that time, approximately two thirds of the total predicted person-years of follow-up between enrollment and the 24-month study visit had been completed. The study definitively showed that the DNA/rAd5 vaccine regimen did not reduce either HIV-1 acquisition or the viral-load set point, as compared with placebo. Although the greater loss to follow-up in the placebo group had borderline significance, the result with respect to vaccine efficacy was not sensitive to this differential (Section 1.6.5 in the Supplementary Appendix). The use of antiretroviral prophylaxis was infrequent and did not appear to affect the results.

The between-group differences in the number of HIV-1 infections in the week 28+ primary analysis (27 in the vaccine group and 21 in the placebo group) and the total number of infections in the modified intention-to-treat analysis (41 in the vaccine group and 31 in the placebo group) were not significant. There were no significant between-group differences in behavioral risk. The rAd5 vector that we used in this study differed substantially from that used in the Step study, since it had deletions in more of the adenovirus genome and included HIV-1 gene inserts coding for Env. Follow-up of the study participants, with the accompanying caveats of potential bias, continues to further assess HIV-1 acquisition in the study cohort after unblinding. In the first planned updated analysis on September 3, 2013, the numbers of week 28+ infections were 29 in the vaccine group and 26 in the placebo group (estimated hazard ratio, 1.09; 95% CI, 0.64 to 1.84; P=0.76). These data show that the late separation of the estimated cumulative HIV-1 incidence curves after month 21 (Fig. 2, and Fig. S18 and S19 in the Supplementary Appendix) was not sustained and emphasize the importance of participant retention in longer-term follow-up. They also strongly support the conclusion that there is no evidence of an increase in the risk of HIV-1 acquisition in the vaccine group in this study.

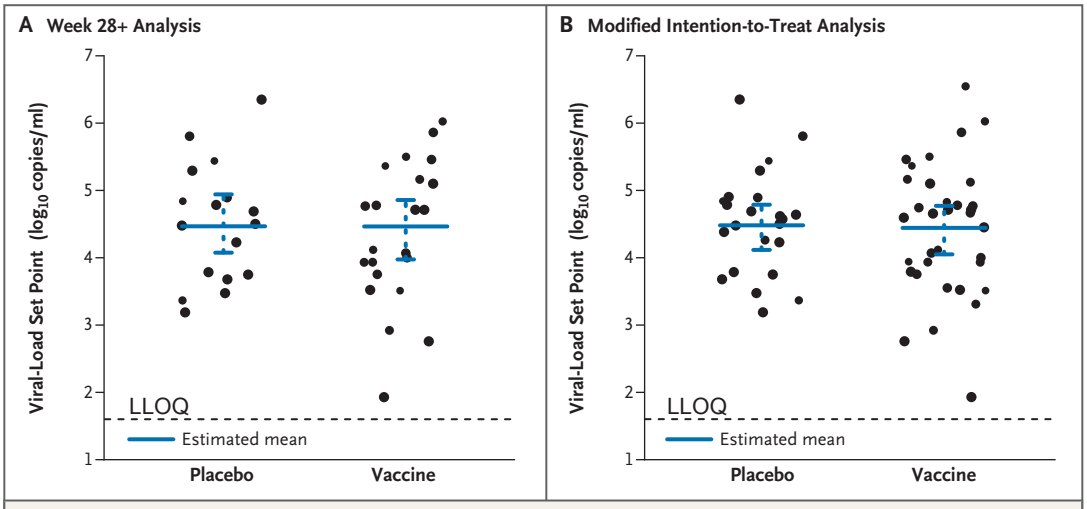

Figure 3. Viral-Load Set Points.

Shown are viral-load set points (the mean plasma HIV-1 RNA level 10 to 20 weeks after diagnosis) among participants with HIV-1 infection diagnosed from week 28 through month 24 (week 28+ infection) (Panel A) and HIV-1 infection in the modified intention-to-treat population (Panel B). The size of each data point reflects the number of measurements used to compute the mean viral-load set point, which is indicated by the horizontal blue line, with a median of 4 measurements (range, 1 to 5). The dashed line indicates the lower limit of quantification (LLOQ) of the viral-load assay (40 copies per milliliter). The I bars indicate 95% confidence intervals.

The DNA/rAd5 vaccine regimen induced both cellular and humoral responses, but these results were not associated with protection in this trial. The CD4+ and CD8+ T-cell response profiles in the random sample of HIV-uninfected participants who were evaluated in this study were similar to those seen among U.S. participants in the HVTN 204 study (a phase 2a study of the same vaccine regimen), who were Ad5-seronegative, thus confirming the immunogenicity profile of this regimen.[24] IgG-binding–antibody responses to gp140 were strong, but responses to the V1-V2 loop of gp120 were substantially lower than those seen in the RV144 trial,[27] in which V1-V2 IgG was a correlate of a reduced risk of HIV acquisition. IgA-binding antibodies to gp140 were higher than those seen in the RV144 trial, in which this measurement was shown to be a correlate of an increased risk of HIV acquisition.[27] Detailed analyses of the quality and breadth of vaccine-induced immune responses in this study and other efficacy trials will be required to further define these and other correlates of risk. Our study gave a definitive, albeit disappointing, result but should provide useful information as newer vaccine regimens and approaches are developed.[35]

The views expressed in this article are those of the authors and do not necessarily represent the official views of the National Institutes of Health (NIH).

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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