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Vaccine Efficacy of ALVAC-HIV and Bivalent Subtype C gp120–MF59 in Adults

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ABSTRACT

BACKGROUND

A safe, effective vaccine is essential to eradicating human immunodeficiency virus (HIV) infection. A canarypox–protein HIV vaccine regimen (ALVAC-HIV plus AIDSVAX B/E) showed modest efficacy in reducing infection in Thailand. An analogous regimen using HIV-1 subtype C virus showed potent humoral and cellular responses in a phase 1–2a trial in South Africa. Efficacy data and additional safety data were needed for this regimen in a larger population in South Africa.

METHODS

In this phase 2b–3 trial, we randomly assigned 5404 adults without HIV-1 infection to receive the vaccine (2704 participants) or placebo (2700 participants). The vaccine regimen consisted of injections of ALVAC-HIV at months 0 and 1, followed by four booster injections of ALVAC-HIV plus bivalent subtype C gp120–MF59 adjuvant at months 3, 6, 12, and 18. The primary efficacy outcome was the occurrence of HIV-1 infection from randomization to 24 months.

RESULTS

In January 2020, prespecified criteria for nonefficacy were met at an interim analysis; further vaccinations were subsequently halted. The median age of the trial participants was 24 years; 70% of the participants were women. The incidence of adverse events was similar in the vaccine and placebo groups. During the 24-month follow-up, HIV-1 infection was diagnosed in 138 participants in the vaccine group and in 133 in the placebo group (hazard ratio, 1.02; 95% confidence interval, 0.81 to 1.30; P=0.84).

CONCLUSIONS

The ALVAC–gp120 regimen did not prevent HIV-1 infection among participants in South Africa despite previous evidence of immunogenicity. (HVTN 702 ClinicalTrials.gov number, NCT02968849.)

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*A complete list of HVTN 702 Study Team members is provided in the Supplementary Appendix, available at NEJM.org.

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Most of the 75.7 million persons with human immunodeficiency virus (HIV) infection worldwide are in sub-Saharan Africa, where subtype C of HIV type 1 (HIV-1) is prevalent.[1] A disproportionately large number of persons with HIV-1 (approximately 7.9 million) live in South Africa, which highlights the urgent need for a vaccine in this country and elsewhere.[2]

In 2010, after the announcement that the community-based RV144 HIV vaccine trial had shown 31% efficacy in Thailand,[3] the Pox Protein Public–Private Partnership (P5) was established. The P5 developed an analogous regimen with the use of HIV-1 subtype C sub-Saharan African strains, including a transmitted-founder isolate.[4] The vaccines, which were administered sequentially, were a recombinant canarypox vector containing subtype C envelope ALVAC-HIV (vCP2438) and an MF59-adjuvanted subtype C bivalent glycoprotein 120 (gp120) vaccine. In a phase 1–2a trial, this vaccine regimen was found to be safe and induced strong humoral and cellular immune responses.[5] In the phase 2b–3 HIV Vaccine Trials Network (HVTN) 702 trial, we investigated the safety and efficacy of this vaccine regimen with respect to HIV-1 acquisition in South Africa.

METHODS

TRIAL DESIGN AND RANDOMIZATION

From October 26, 2016, to June 21, 2019, we conducted this randomized, double-blind, placebo-controlled trial at 14 sites in South Africa. The research ethics committees of the University of the Witwatersrand, University of Cape Town, University of KwaZulu-Natal, Sefako Makgatho University, and the South African Medical Research Council approved the trial.

Participants were randomly assigned in a 1:1 ratio to receive the vaccine regimen or placebo, stratified according to sex and site, with centrally generated randomization by the Statistical Center for HIV–AIDS Research and Prevention (SCHARP). The trial was designed to evaluate vaccine efficacy to prevent HIV-1 infection within 24 months after enrollment, with formal monitoring for potential harm, nonefficacy, and high efficacy, with potential to extend follow-up to 36 months for all participants.[6]

TRIAL POPULATION

Eligible participants were healthy adults between the ages of 18 and 35 years without HIV-1 infection. We aimed to have a trial population in which 60 to 75% of the participants were women. (In this report, women and men are identified according to the sex they were assigned at birth.) Women who had reproductive potential were required to use contraception until 3 months after the final vaccination; pregnant or breast-feeding women were excluded from the trial. All the participants provided written informed consent in their preferred language.

INTERVENTION

The vaccine regimen consisted of an ALVAC-HIV vector and an MF59-adjuvanted bivalent subtype C gp120. ALVAC-HIV (vCP2438) (at a dose of 10^7 50% cell-culture infectious dose) expresses the HIV-1 envelope glycoprotein of the subtype C ZM96.C strain, along with the gp41 transmembrane sequence, *gag*, and *protease* from the subtype B LAI strain. Bivalent subtype C gp120 is a combination of 100 μg each of the HIV-1 subtype C gp120 of the TV1.C and 1086.C strains. Placebo consisted of 0.9% sodium chloride.

Participants received an intramuscular injection of ALVAC-HIV or placebo at months 0 and 1, which was followed by four injections of ALVAC-HIV plus bivalent subtype C gp120–MF59 or placebo at months 3, 6, 12, and 18. ALVAC-HIV or placebo was administered in the left deltoid, and bivalent subtype C gp120–MF59 or placebo was administered in the right deltoid.

PRIMARY AND SECONDARY OUTCOMES

The primary efficacy outcome was the occurrence of HIV-1 infection from randomization to 24 months. The primary analysis was conducted in the modified intention-to-treat population, which included all the participants who had undergone randomization with the exception of those in whom HIV-1 infection had been diagnosed at the time of enrollment.

Secondary analyses were performed in different cohorts and over different time periods. The first secondary analysis was performed in a cohort of participants who were HIV-1–negative at month 6.5 (i.e., 2 weeks after the fourth vaccination) and were at risk for subsequent HIV-1 infection (month 6.5 at-risk cohort). These participants

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were evaluated between month 6.5 and month 24. The second secondary analysis of vaccine efficacy was performed between randomization and month 36 in the modified intention-to-treat population. The third secondary efficacy analysis was performed between month 6.5 and month 24 in the per-protocol cohort, which included participants in the month 6.5 at-risk cohort who had received the first four vaccinations on schedule and without error. Follow-up time was the number of days from randomization or the month 6.5 visit until the diagnosis of HIV-1 infection or, in participants without such a diagnosis, from randomization or the month 6.5 visit to the last negative test at the end of the evaluation period for that outcome, whichever occurred first. Safety analyses included all the participants who had undergone randomization and received at least one injection of vaccine or placebo and were performed according to the injection received.

OUTCOME EVALUATION

Trial visits were scheduled at months 0, 1, 3, 6, 6.5, 12, 12.5, 15, 18, 18.5, and 21 and every 3 months thereafter up to month 36 and included evaluations of vaccine safety. (Details regarding these evaluations are provided in the protocol and the Supplementary Appendix, available with the full text of this article at NEJM.org.) At each visit, we performed a physical examination, counseling regarding HIV risk reduction, pregnancy assessment, assessment of the social effect of participation in the vaccine trial, monitoring of adverse events, and information regarding concomitant medications. HIV testing with counseling occurred every 3 months, testing for sexually transmitted infection was performed every 6 months, and a behavioral-risk questionnaire was administered at screening and at months 6.5, 12, 24, and 36. Access to free preexposure prophylaxis and postexposure prophylaxis (PrEP–PEP) was provided. Trial vaccinations were prohibited in women who became pregnant or initiated breast-feeding during the trial.

LABORATORY METHODS

Testing for HIV types 1 and 2 was performed at trial sites to avoid potential unblinding of trial-group assignments. HIV infection was confirmed by detection of HIV nucleic acid, and HIV-1 RNA viral loads were measured after diagnosis. An independent adjudication committee reviewed the results of HIV diagnostic testing from specimens collected on at least two dates and made the primary determination regarding infection status and timing. For monitoring the use of PrEP–PEP, dried blood-spot samples were obtained from all the participants who were seen at sites on a given day each month to measure levels of tenofovir diphosphate (TFV-DP).

TRIAL OVERSIGHT

The trial was overseen by the data and safety monitoring board of the National Institute of Allergy and Infectious Diseases (NIAID). This board provided recommendations to the HVTN 702 oversight group (which consisted of representatives of the NIAID, HVTN, Bill and Melinda Gates Foundation, Sanofi Pasteur, and GSK), who advised the protocol team and made the final decisions regarding conduct of the trial. All data were collected and analyzed by SCHARP. All the authors had access to the data, conducted a critical review of the manuscript, and approved the decision to submit the manuscript for publication. The first draft of the manuscript was written by the first three authors, the statisticians, and the last author.

STATISTICAL ANALYSIS

We determined that a sample size of 5400 participants would provide a power of at least 90% to reject a null hypothesis of vaccine efficacy between randomization and 24 months (the primary measure of vaccine efficacy) of 25% or less if the true vaccine efficacy was 50% or more, assuming an annual HIV-1 incidence of 4% in the placebo group (Tables S2 and S3 in the Supplementary Appendix). Vaccine efficacy was calculated as 1 minus the hazard ratio for HIV-1 infection, which we estimated using a sex-stratified Cox proportional-hazards model and tested using a sex-stratified log-rank test. We also measured vaccine efficacy using a ratio of cumulative incidences of HIV-1 infection in the vaccine group as compared with the placebo group; we calculated this measure using Nelson–Aalen cumulative hazard estimates. We used the Kaplan–Meier method to estimate the cumulative incidence of HIV-1 infection and loss to follow-up. We performed Wald interaction tests to evaluate prespecified baseline variables as modifiers of

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vaccine efficacy, using stratified Cox proportional-hazards models and the Holm method[7] to adjust for multiple comparisons.

We monitored for a potential increase in the risk of HIV-1 infection induced by the vaccine, beginning after the diagnosis of 12 infections and continuing until the initiation of nonefficacy monitoring, which began after the diagnosis of 59 infections. The prespecified stopping criteria for nonefficacy were a lower limit of the 95% confidence intervals of less than 0% and an upper limit of less than 40% in both the modified intention-to-treat population and the month 6.5 at-risk cohort on the basis of both the Cox proportional-hazards analysis and the cumulative-incidence-ratio estimation. Nonefficacy criteria also required that at least 60% of the enrolled participants had reached the month 18.5 visit.

All P values are two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. Additional details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

TRIAL PARTICIPANTS

During the trial period, 9918 persons were screened and 5407 were enrolled (Fig. S1). Of these participants, 3 were enrolled twice, and only data from the first enrollment were used. Of the 5404 unique participants enrolled, 2704 were assigned to the vaccine group and 2700 to the placebo group. The cutoff date for the data that are presented here was February 18, 2020, before the unblinding of the trial on February 19, 2020.

Data regarding demographic and clinical characteristics and HIV-1 risk factors were similar in the two trial groups (Table 1). Overall, 3786 participants (70%) were female, and of these women, 1115 (29%) were between the ages of 18 and 21 years. Male participants tended to be older, with 859 of 1618 (53%) at least 26 years of age. At enrollment, sexually transmitted diseases were diagnosed in 1003 of 3389 women (30%) and in 228 of 1254 men (18%). Detailed characteristics of the participants at baseline are provided in Tables S4 through S9.

The modified intention-to-treat cohort included 5384 participants (2695 in the vaccine group and 2689 in the placebo group) who were followed for a median of 623 days (interquartile range [IQR], 427 to 819). The median follow-up was 642 days (IQR, 459 to 756) in the month 6.5 at-risk cohort and 644 days (IQR, 461 to 756) in the per-protocol cohort. The rate of loss to follow-up was 3.9 per 100 person-years in each of the two groups (Fig. S2). Adherence to the protocol was high among the participants (Tables S10 and S11).

EFFICACY AGAINST HIV-1 INFECTION

During the first 24 months of follow-up, 138 HIV-1 infections occurred in the vaccine group and 133 in the placebo group, for an estimated incidence rate of 3.4 per 100 person-years (95% confidence interval [CI], 2.8 to 4.0) and 3.3 per 100 person-years (95% CI, 2.8 to 3.9), respectively (hazard ratio, 1.02; 95% CI, 0.81 to 1.30; P=0.84) (Fig. 1A and Table 2). The incidence of HIV-1 infection was similar in the vaccine group and the placebo group in secondary analyses during 36 months of follow-up (hazard ratio, 1.05; 95% CI, 0.83 to 1.31), in the month 6.5 at-risk cohort between 6.5 months and 24 months (hazard ratio, 1.15; 95% CI, 0.84 to 1.58), and in the per-protocol cohort, as well as in other secondary analyses (Figs. S3 through S9).

Between randomization and month 24, the vaccine efficacy according to sex was similar in the two groups (P=0.92 for interaction); the estimated hazard ratio was 1.03 (95% CI, 0.80 to 1.33) among women and 0.99 (95% CI, 0.50 to 1.98) among men (Fig. 2A and Table 2). The rate of HIV-1 infection among women was 4.3 per 100 person-years (95% CI, 3.6 to 5.2) in the vaccine group and 4.2 per 100 person-years (95% CI, 3.5 to 5.0) in the placebo group; the respective rates among men were 1.3 per 100 person-years (95% CI, 0.7 to 2.0) and 1.3 per 100 person-years (95% CI, 0.7 to 2.1).

Secondary analyses also included prespecified assessments of potential modifications in vaccine efficacy among women according to age, baseline HIV-1 risk score, body-mass index, and geographic region from randomization to month 24. None of these factors were found to modify the vaccine efficacy after adjustment for multiple comparisons (P≥0.09) (Table S12).

POSTINFECTION VIRAL LOAD

Among the 294 participants who were included in the modified intention-to-treat population and

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Table 1. Characteristics of the Participants at Baseline, According to Sex.*

Characteristic	Women			Men		
	Total (N=3786)	Vaccine (N=1893)	Placebo (N=1893)	Total (N=1618)	Vaccine (N=811)	Placebo (N=807)
Age group — no. (%)						
18–21 yr	1115 (29)	543 (29)	572 (30)	321 (20)	166 (20)	155 (19)
22–25 yr	1420 (38)	723 (38)	697 (37)	438 (27)	219 (27)	219 (27)
26–35 yr	1251 (33)	627 (33)	624 (33)	859 (53)	426 (53)	433 (54)
Body-mass index — no. (%)†						
<18.5	133 (4)	56 (3)	77 (4)	232 (14)	114 (14)	118 (15)
18.5–24	1406 (37)	725 (38)	681 (36)	1127 (70)	560 (69)	567 (70)
25–29	978 (26)	493 (26)	485 (26)	194 (12)	97 (12)	97 (12)
≥30	1269 (34)	619 (33)	650 (34)	65 (4)	40 (5)	25 (3)
Gender identity — no. (%)						
Female	3783 (100)	1892 (100)	1891 (100)	6 (<1)	5 (1)	1 (<1)
Male	2 (<1)	1 (<1)	1 (<1)	1598 (99)	801 (99)	797 (99)
Transgender female or male	1 (<1)	0	1 (<1)	10 (1)	4 (<1)	6 (1)
Gender variant	0	0	0	2 (<1)	1 (<1)	1 (<1)
Prefer not to answer	0	0	0	2 (<1)	0	2 (<1)
Condom use — no. (%)						
Always	209 (6)	88 (5)	121 (6)	140 (9)	79 (10)	61 (8)
Sometimes	2790 (74)	1411 (75)	1379 (73)	1228 (76)	601 (74)	627 (78)
Never	786 (21)	393 (21)	393 (21)	249 (15)	130 (16)	119 (15)
Exchange of sex for money or gifts in past 30 days — no. (%)	791 (21)	384 (20)	407 (22)	256 (16)	128 (16)	128 (16)
Number of sex acts in past 30 days — no. (%)						
0–4	1238 (33)	624 (33)	614 (32)	455 (28)	229 (28)	226 (28)
5–10	1373 (36)	702 (37)	671 (35)	609 (38)	310 (38)	299 (37)
≥11	1173 (31)	567 (30)	606 (32)	554 (34)	272 (34)	282 (35)
Lives with spouse or main partner — no. (%)	530 (14)	239 (13)	291 (15)	278 (17)	144 (18)	134 (17)
Sexually transmitted infection — no./total no. (%)‡						
Syphilis	44/3389 (1)	21/1702 (1)	23/1687 (1)	26/1252 (2)	10/633 (2)	16/619 (3)
Neisseria gonorrhoeae	179/3389 (5)	90/1702 (5)	89/1687 (5)	39/1252 (3)	19/633 (3)	20/619 (3)
Chlamydia trachomatis	779/3389 (23)	408/1702 (24)	371/1687 (22)	199/1252 (16)	103/633 (16)	96/619 (16)
Trichomonas vaginalis	192/3389 (6)	97/1702 (6)	95/1687 (6)	NA	NA	NA

* Percentages may not total 100 because of rounding. NA denotes not applicable.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Testing for sexually transmitted infections was introduced in version 2 of the protocol, so data are not available for 763 trial participants (397 women and 366 men).

who were found to have HIV-1 infection during 36 months of follow-up, the mean $\log_{10}$ viral load at the time of diagnosis was similar in the vaccine group and in the placebo group, with 4.82 $\log_{10}$ copies per milliliter (95% CI, 4.61 to 5.02) and 4.64 $\log_{10}$ copies per milliliter (95% CI, 4.45 to 4.84), respectively (Table S13 and Fig. S10). The median time until the initiation of

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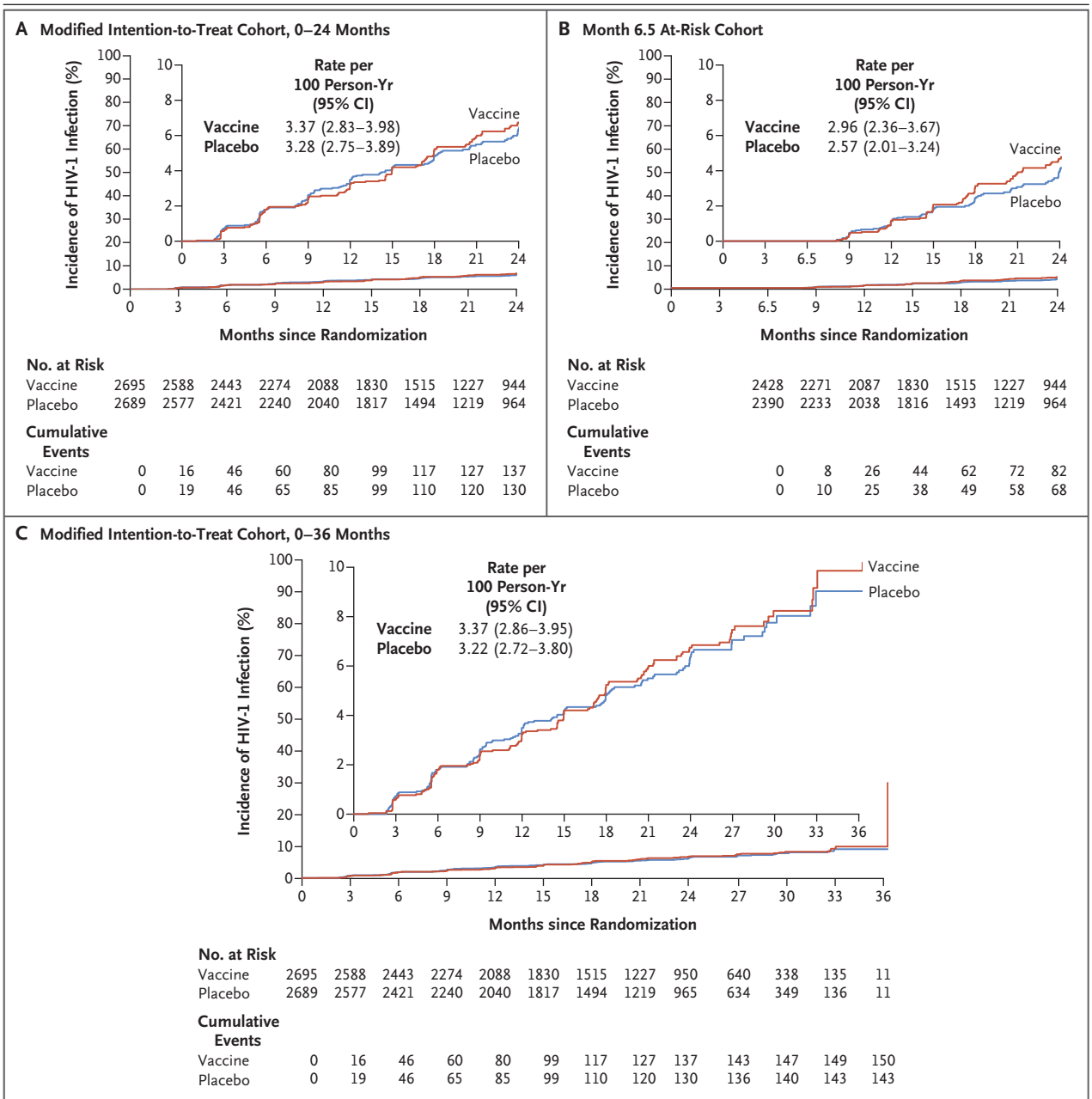

Figure 1. Kaplan–Meier Analysis of HIV-1 Infection in Three Cohorts.

Shown are data for the cumulative incidence of human immunodeficiency virus type 1 (HIV-1) infection among the participants in the modified intention-to-treat cohort who were evaluated during the period from randomization to 24 months (primary analysis cohort) (Panel A), in the cohort of participants who were HIV-1–negative at month 6.5 and were at risk for subsequent HIV-1 infection (month 6.5 at-risk cohort) (Panel B), and in the modified intention-to-treat cohort during the period from randomization to month 36 (Panel C). The apparent uptick in the vaccine curve at month 36 is due to a single infection among the remaining 11 participants at risk. In each panel, the inset shows the same data on an expanded y axis; in Panel C, the vaccine curve at 36 months has been cut off at 10% for graphical presentation.

antiretroviral therapy was 13 weeks in the vaccine group and 14 weeks in the placebo group (Fig. S11).

USE OF PREP–PEP

Despite the availability of PrEP–PEP at no cost to all the participants, the overall use of PrEP as

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Table 2. Rate of HIV-1 Infection and Estimated Hazard Ratios, According to Cohort and Baseline Variables.*

Cohort and Time Period	Vaccine (N=2695)				Placebo (N=2689)				Hazard Ratio (95% CI)†
	Participants Evaluated	Infections Diagnosed	Person-Yrs	Infection Rate	Participants Evaluated	Infections Diagnosed	Person-Yrs	Infection Rate	
		number		*number/100 person-yr*		*number*		*number/100 person-yr*	
mITT cohort (mo 0–24)	2695	138	4098.3	3.4	2689	133	4052.7	3.3	1.02 (0.81–1.30)
mITT cohort (mo 0–36)	2695	151	4477.9	3.4	2689	143	4438.7	3.2	1.05 (0.83–1.31)
Month 6.5 at-risk cohort (mo 6.5–24)	2430	83	2804.0	3.0	2393	71	2760.6	2.6	1.15 (0.84–1.58)
Sex of participants in the mITT cohort (mo 0–24)									
Female	1887	122	2819.9	4.3	1886	117	2787.3	4.2	1.03 (0.80, 1.33)
Male	808	16	1278.4	1.3	803	16	1265.5	1.3	0.99 (0.50, 1.98)
Age of women in the mITT cohort (mo 0–24)									
≤25 yr	1264	87	1832.1	4.7	1267	80	1829.6	4.4	1.08 (0.80, 1.47)
>25 yr	623	35	987.8	3.5	619	37	957.7	3.9	0.92 (0.58, 1.46)

* Data are shown for the modified intention-to-treat (mITT) cohort during the period from randomization to 24 months (primary analysis), in the mITT cohort from randomization to 36 months (secondary analysis), in the month 6.5 at-risk cohort consisting of the mITT participants who were HIV-1–negative at 6.5 months and at risk for subsequent HIV-1 infection (secondary analysis), and in the mITT cohort according to sex and age among the female participants.

† The listed values are hazard ratios for vaccine as compared with placebo, as estimated by the Cox proportional-hazards model. In addition to hazard ratios, cumulative incidence ratio (CIR) estimates were calculated for vaccine efficacy in the mITT cohort during the period from month 0 to 24 (1.03; 95% CI, 0.81 to 1.31), in the mITT cohort from month 0 to 30 (1.05; 95% CI, 0.81 to 1.36), and in the month 6.5 at-risk cohort (1.12; 95% CI, 0.81 to 1.54). The 30-month analysis corresponds to the 36-month analysis by the Cox proportional-hazards model but was estimated over the time period in which there were at least 150 participants at risk in each trial group.

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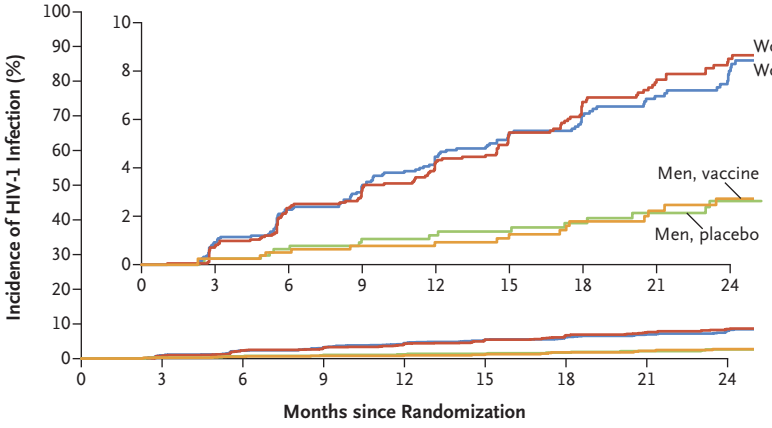
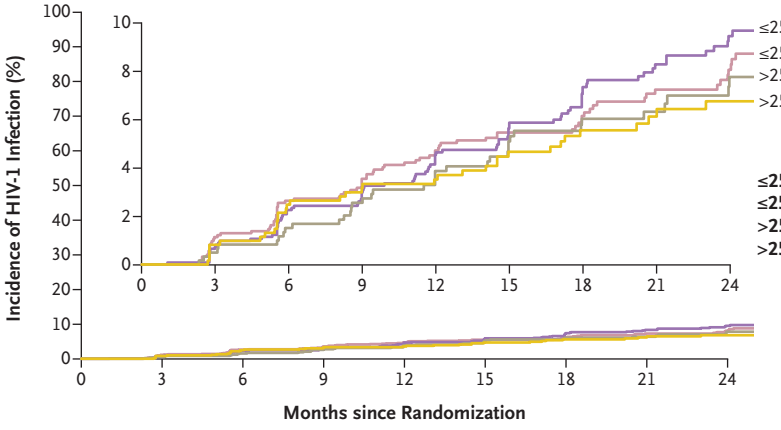
A Modified Intention-to-Treat Cohort, According to Sex



Rate per 100 Person-Yr (95% CI)	
Women, Vaccine	4.33 (3.59–5.17)
Women, Placebo	4.20 (3.47–5.03)
Men, Vaccine	1.25 (0.72–2.03)
Men, Placebo	1.26 (0.72–2.05)

No. at Risk									
Women, vaccine	1887	1804	1696	1582	1446	1247	1015	815	632
Women, placebo	1886	1800	1684	1554	1409	1233	1002	801	642
Men, vaccine	808	784	747	692	642	583	500	412	312
Men, placebo	803	777	737	686	631	584	492	418	322
Cumulative Events									
Women, vaccine	0	14	42	54	73	90	105	113	121
Women, placebo	0	17	41	57	76	89	98	106	114
Men, vaccine	0	2	4	6	7	9	12	14	16
Men, placebo	0	2	5	8	9	10	12	14	16

B Modified Intention-to-Treat Cohort, According to Women's Age



Rate per 100 Person-Yr (95% CI)	
≤25 Yr of Age, Vaccine	4.75 (3.80–5.86)
≤25 Yr of Age, Placebo	4.37 (3.47–5.44)
>25 Yr of Age, Vaccine	3.54 (2.47–4.93)
>25 Yr of Age, Placebo	3.86 (2.72–5.33)

No. at Risk									
≤25 Yr of age, vaccine	1264	1203	1120	1030	926	791	640	515	401
≤25 Yr of age, placebo	1267	1206	1116	1015	917	800	640	514	415
>25 Yr of age, vaccine	623	601	576	552	520	456	375	300	231
>25 Yr of age, placebo	619	594	568	539	492	433	362	287	227
Cumulative Events									
≤25 Yr of age, vaccine	0	9	27	35	52	63	74	80	86
≤25 Yr of age, placebo	0	14	32	42	54	61	66	73	77
>25 Yr of age, vaccine	0	5	15	19	21	27	31	33	35
>25 Yr of age, placebo	0	3	9	15	22	28	32	33	37

Figure 2. Kaplan–Meier Analysis of HIV-1 Infection, According to Sex and Women's Age.

Shown is the cumulative incidence of HIV-1 infection in the modified intention-to-treat cohort during the period from randomization to 24 months, according to two prespecified baseline variables: sex (Panel A) and women's age (Panel B). In each panel, the inset shows the same data on an expanded y axis.

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reported by the participants was low (in 120 women [3%] and 52 men [3%]), as was the use of PEP (in 91 women [2%] and 80 men [5%]) (Table S14). Of the 2405 samples of dried-blood spots that were collected, TFV-DP levels were detectable in 51 samples (2%) and reached effective levels in 5 (<1%) (Tables S15 and S16). Overall, PrEP–PEP was detected during an estimated 2% of person-years of follow-up in the vaccine group and 3% of person-years in the placebo group.

SAFETY, REACTOGENICITY, AND DEATH

The incidence of inaccurate administration of vaccine or placebo was low, with errors occurring in 3 of 2704 participants in the vaccine group and in 2 of 2700 participants in the placebo group. In general, vaccinations were safe and had an acceptable side-effect profile, as reported by the participants (Tables S17, S18, and S19). Vaccine recipients were more likely than placebo recipients to report reactogenicity (46% vs. 33%, P<0.001), with pain or tenderness at the injection site most frequently reported by vaccine recipients (23%) and headache reported most frequently by placebo recipients (16%). Most symptoms were mild. The number and frequency of adverse events were well balanced in the two groups (Table S20).

Adverse events that were deemed by investigators to be related to the injection were uncommon but were more frequent among the vaccine recipients than among the placebo recipients (1% vs. <1%, P<0.001). The few related adverse events that resulted in discontinuation included generalized rash (1 in the vaccine group and 2 in the placebo group), generalized urticaria or cellulitis (1 each in the vaccine group), and diarrhea or headache (1 each in the placebo group). Eighteen deaths, all deemed by the investigators to be unrelated to the trial agent, were reported in 8 vaccine recipients and in 10 placebo recipients. Details regarding deaths are provided in the Additional Safety Data and Analyses section in the Supplementary Appendix.

PREGNANCY

A total of 163 pregnancies were reported (82 in the vaccine group and 81 in the placebo group), which resulted in an annual pregnancy incidence of less than 3%. In 78 of these women (48%), oral hormonal contraception was the method last reported. No congenital anomalies were reported.

DISCUSSION

In the HVTN 702 trial, we found no significant effect of the vaccine regimen on the acquisition of HIV-1 infection in a well-powered evaluation involving 5404 participants. In an interim analysis performed in January 2020, the trial met the prespecified stopping criteria for nonefficacy with no safety concerns. At that time, the data and safety monitoring board recommended that vaccinations be stopped with unblinding of the results; all the participants were to be followed for 1 year after the last vaccination.

Several components of the vaccine regimen that we used in our trial differed from those used in the vaccine regimen of the earlier RV144 trial. These included the use of different vector vaccine gene-sequence inserts (the subtype C ZM96 strain of gp120, which was inserted into the HVTN 702 vector vaccine, as compared with the subtype CRF01_AE 92TH023 strain of gp120 that was inserted into the RV144 vector vaccine), a different protein vaccine sequence (subtype 1086 and TV1 strains, as compared with subtype CRF01_AE A244 and subtype B MN strains in RV144), the use of different adjuvants (MF59, as compared with aluminum hydroxide in RV114), and the use of additional booster injections in the HVTN 702 trial at 12 and 18 months.[8-10] Differing patterns of immunogenicity have been seen in studies comparing the two regimens in South Africa. The HVTN 100 trial evaluated the immunogenicity of the regimen that we used in the HVTN 702 trial for comparison with the HVTN 097 trial, which evaluated the regimen used in the RV144 trial.[11] Levels of binding and functional antibodies to gp120 and gp140 antigens and T-cell responses to vaccine-matched peptide pools were greater with the HVTN 702 regimen (as assessed in the HVTN 100 trial) than with the RV114 regimen (as assessed in both the RV114 trial and the HVTN 097 trial).[11-13] However, antibody responses in the V2 region were higher with the RV144 regimen than with the subtype C vaccine regimen.[11] The V2 region responses were important correlates of risk in the RV144 trial.[12] The substantial differences in antibody specificities induced by vaccination in these

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two regimens suggest that viral sequences or adjuvants may influence the elicitation of V2-specific antibodies, with higher values associated with decreased HIV-1 risk.[14]

The incidence of HIV-1 acquisition (and thus potentially of HIV-1 exposure) was markedly higher in our trial than in the RV144 trial. Given the high prevalence of sexually transmitted infections among the women in our trial, it is likely that genital tract inflammation was also prevalent.[15] The HIV-1 incidence of 4.2% among the women in the placebo group in our trial was 14 times that seen among women in the placebo group in the RV144 trial (0.3%). This incidence reflects hyperendemic HIV-1 transmission in the community, probably from the high frequency of acute infections and low rates of viral suppression.[16] In the RV144 trial, a lower vaccine efficacy was observed among participants at high risk for HIV-1 acquisition than among those at low or moderate risk.[17] In nonhuman primates that were vaccinated with ALVAC–gp120, better protection from experimental mucosal infection was achieved with exposure to a low viral dose than with a high-dose challenge,[18] which provides a possible explanation for the role that the force of infection (i.e., the level of infectiousness, as defined by the amount of exposure to persons with viremia) plays in overcoming vaccine-induced immunity. We did not find vaccine efficacy in any subgroup, even among the participants who were determined to have a low risk of HIV-1 acquisition on the basis of the diagnosis of sexually transmitted infections and behavioral data. However, the eligibility criteria and high burden of HIV-1 infection in South Africa would suggest that few women who were actually at low risk were enrolled in the trial.

The genetic diversity of the sub-Saharan African subtype C epidemic was substantially greater than that in the epidemic of HIV subtype A/E in Thailand 15 years earlier, when the RV144 trial was conducted, a factor that is also likely to have played a role in the differential efficacy between the two trials. The vaccine efficacy in the RV144 trial was found to depend on viral genetics, especially with respect to whether the exposing HIV-1 strain matched the vaccine insert at amino acid position 169 (which was lysine) in the V2 loop.[19] Studies suggest that the frequency of such a match to the HVTN 702 vaccine is much less common in South Africa than in Thailand.[20] The match of the V1V2 region of the HVTN 702 vaccine components with circulating sequences in South Africa, as compared with their Thai counterparts in the RV144 trial, is also less common on the basis of HIV-1 sequencing data from the Los Alamos National Laboratory database[21] (Fig. S12).

In addition, host genetic factors that may influence vaccine efficacy also differ between the South African and Thai populations. Data from the RV144 trial suggest that vaccine efficacy depends on the presence or absence of *FCGR2C* and the HLA-A*02 genotype.[22-24] Recent data suggest that South Africa has a relatively low prevalence of genotypes of the fragment crystallizable region (the portion of an antibody that is involved in immune activation) and human leukocyte antigen class I that were associated with the high vaccine efficacy in the RV144 trial (Table S21).[25-27]

Limitations of our trial include the inability to directly compare the regimens used in the RV144 and HVTN 702 trials to address differences in the use of vectors, adjuvants, and proteins. The absence of an available immunologic biomarker to predict protection further compounds our inability to infer whether differences in efficacy are explained by observed differences in immunogenicity or by other factors, such as infection force and viral diversity. Additional studies on the immunologic characteristics and viral sequences are under way to improve our understanding of the results and implications for this field of research. Thus, isolating which factor or combination of factors is responsible for the different efficacy results in the two trials will be challenging, given the differences between the vaccines and the immune responses they generated, along with the differences in the levels of viral exposure, the extent of matching between the vaccines and the exposing viruses, and in host genetics and other host factors.

Despite promising immunogenicity, this canarypox–protein HIV vaccine regimen was not efficacious in preventing the acquisition of HIV-1 infection in our trial population in South Africa. The high HIV-1 incidence that we observed in our trial illustrates the unrelenting aspect of the epidemic, especially among young women. More than ever, an effective vaccine to prevent HIV-1 acquisition in diverse populations is needed.

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APPENDIX

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