Mosaic HIV-1 vaccine regimen in southern African women (Imbokodo/HVTN 705/HPX2008): a randomised, double-blind, placebo-controlled, phase 2b trial

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Summary

Background HIV type 1 (HIV-1) remains a global health concern, with the greatest burden in sub-Saharan Africa. Despite 40 years of research, no vaccine candidate has shown durable and protective efficacy against HIV-1 acquisition. Although pre-exposure prophylaxis in groups with high vulnerability can be very effective, barriers to its use, such as perceived low acquisition risk, fear of stigma, and concerns about side-effects, remain. Thus, a population-based approach, such as an HIV-1 vaccine, is needed. The current study aimed to evaluate the efficacy and safety of a heterologous HIV-1 vaccine regimen, consisting of a tetravalent mosaic adenovirus 26-based vaccine (Ad26.Mos4.HIV) and aluminium phosphate-adjuvanted clade C glycoprotein (gp) 140, in young women at risk of acquiring HIV-1 in southern Africa.

Methods This randomised, double-blind, phase 2b study enrolled sexually active women without HIV-1 or HIV-2 aged 18–35 years at 23 clinical research sites in Malawi, Mozambique, South Africa, Zambia, and Zimbabwe. Participants were centrally randomly assigned (1:1) to receive intramuscular injections of vaccine or saline placebo in stratified permuted blocks via an interactive web response system. Study participants, study site personnel (except those with primary responsibility for study vaccine preparation and dispensing), and investigators were masked to treatment group allocation. The vaccine regimen consisted of Ad26.Mos4.HIV administered at months 0 and 3 followed by Ad26.Mos4.HIV administered concurrently with aluminium phosphate-adjuvanted clade C gp140 at months 6 and 12. The primary efficacy outcome was vaccine efficacy in preventing laboratory-confirmed HIV-1 acquisition diagnosed between visits at month 7 and month 24 after the first vaccination (VE[7–24]) in the per-protocol population, which included participants who had not acquired HIV-1 4 weeks after the third vaccination, received all planned vaccinations at the first three vaccination visits within the protocol-specified windows, and had no major protocol deviations that could affect vaccine efficacy. Primary safety outcomes were assessed in randomly assigned participants who received one study injection or more based on the actual injection received. The primary safety endpoints were the incidences of unsolicited adverse events (AEs), solicited local and systemic AEs, serious AEs, AEs of special interest, and AEs leading to discontinuation of vaccination. This trial is registered with ClinicalTrials.gov, NCT03060629, and is complete.

Findings Between Nov 3, 2017, and June 30, 2019, 2654 women were randomly assigned, of whom 2636 women (median age of 23 years [IQR 20–25]) were enrolled and received at least one study injection (1313 assigned vaccine, 1323 placebo; 1317 received vaccine, 1319 placebo). Analysis of the primary efficacy outcome in the per-protocol cohort included 1080 women in the vaccine group and 1108 women in the placebo group; the incidence of HIV-1 acquisition per 100 person-years over months 7–24 after the first vaccination was 3·38 (95% CI 2·54–4·41) in the vaccine group and 3·94 (3·04–5·03) in the placebo group, with an estimated VE(7–24) of 14·10% (95% CI –22·00 to 39·51; p=0·40). There were no serious unsolicited AEs, AEs of special interest, or deaths related to the study vaccine. In the vaccine group, 663 (50·3%) of 1317 participants had grade 1 or 2 solicited local AEs and ten (0·8%) of 1317 participants had grade 3 or 4 solicited local AEs. In the placebo group, 305 (23·1%) of 1319 participants had grade 1 or 2 solicited local AEs and three (0·2%) of 1319 participants had grade 3 or 4 solicited local AEs. 863 (65·5%) of 1317 participants in the vaccine group had grade 1 or 2 solicited systemic AEs and 34 (2·6%) of 1317 participants had grade 3 or 4 solicited systemic AEs. 763 (57·8%) of 1319 participants in the placebo group had grade 1 or 2 solicited systemic AEs and 20 (1·5%) of 1319 participants had grade 3 or 4 solicited systemic AEs. Overall, three (0·2%) of 1317 participants in the vaccine group and three (0·2%) of 1319 participants in the placebo group discontinued vaccination due to an unsolicited AE, and three (0·2%) of 1317 participants in the vaccine group and one (0·1%) of 1319 participants in the placebo group discontinued vaccination due to a solicited AE.

Interpretation The heterologous Ad26.Mos4.HIV and clade C gp140 vaccine regimen was safe and well tolerated but did not show efficacy in preventing HIV-1 acquisition in a population of young women in southern Africa at risk of HIV-1.

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See Online for appendix

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Introduction

HIV type 1 (HIV-1) remains a global public health concern, with 39 million people living with HIV in 2022, approximately two-thirds of whom were living in sub-Saharan Africa.[1] Moreover, in sub-Saharan Africa, young women are 3 times more likely than young men to acquire HIV.[1] No candidate HIV-1 vaccine has shown durable protective efficacy despite nearly 40 years of vaccine research.[2] Although pre-exposure prophylaxis (PrEP) in groups with high vulnerability can be highly effective, barriers to its use, such as perceived low acquisition risk, fear of stigma, and concerns about side-effects, remain.[1] Thus, a population-based approach, such as an HIV-1 vaccine, is needed.

Research in context

Evidence before this study

An HIV type 1 (HIV-1) vaccine that is safe, effective, and durable continues to be elusive, due in part to the tremendous genetic diversity and propensity for immune evasion of HIV-1.
We searched PubMed on June 27, 2024, for clinical studies assessing the efficacy of HIV-1 vaccines with the search terms (HIV vaccine efficacy) AND (clinical trial[pt]) and found 373 articles. Two versions of a recombinant glycoprotein (gp) 120 subunit vaccine were advanced in the phase 3 VaxGen trials VAX004 (of the AIDSVAX B/B vaccine) and VAX003 (of the AIDSVAX B/E vaccine), but neither showed efficacy in preventing HIV-1 acquisition. RV144, a phase 3 trial involving a prime-boost regimen consisting of a recombinant canarypox vector-based vaccine expressing Gag, Pro, and Env antigens (ALVAC-HIV) and a recombinant bivalent gp120 subunit vaccine (AIDSVAX B/E), administered in Thailand, was the only study to show a modest estimated efficacy (31·2%) in reducing HIV-1 transmission over 42 months, which was statistically significant but not effective enough for licensure. The MRKad5 adenovirus type 5 vaccine expressing Gag, Pol, and Nef antigens was evaluated in phase 2b studies HVTN 502 (the Step Study) and HVTN 503 (Phambili). No efficacy was observed in either HVTN 502 or HVTN 503, and an increased risk of HIV-1 acquisition was seen in all vaccinated participants in HVTN 503 and in a subgroup of male vaccinated participants in HVTN 502 (the efficacy in female participants could not be evaluated due to low HIV-1 acquisition rates). HVTN 505, a phase 2b trial to evaluate a DNA-based regimen plus recombinant adenovirus type 5 vector-based vaccine, found that the vaccine did not prevent HIV-1 acquisition or reduce viral load. Antibody-mediated protection from a VRC01 broadly neutralising antibody infusion was assessed in the phase 2b studies HVTN 703/HPTN 081 and HVTN 704/HPTN 085; no statistically significant overall protective efficacy was observed, although 75·4% protection was seen for some HIV-1 isolates sensitive to VRC01. Uhambo (HVTN 702) was a phase 2b–3 trial conducted in South Africa to evaluate a modified RV144 regimen (ALVAC-HIV and MF59-adjuvanted bivalent subtype C gp120), and interim analysis in February, 2020, showed no protective efficacy against HIV-1 acquisition. Another approach to HIV-1 vaccine development employs an adenovirus 26 (Ad26) vector-based mosaic immunogen approach to elicit a broad immune response. We searched PubMed on June 27, 2024, for studies of mosaic HIV-1 vaccine regimens with the terms (HIV vaccine) AND (mosaic gp140) AND (clinical trial[pt]) and found four articles. Mosaic-based Ad26 vaccines were evaluated in a preclinical model and in a series of clinical studies in populations at low risk for HIV-1. APPROACH (NCT02315703) was a phase 1–2a trial assessing various combinations of trivalent Ad26.Mos.HIV (encoding one mosaic Env antigen and two mosaic Gag–Pol antigens) and modified vaccinia Ankara mosaic vaccines with or without high-dose or low-dose clade C gp140, with the strongest immune responses observed with the Ad26.Mos.HIV vaccine with high-dose clade C gp140. In a companion non-human primate challenge study, Ad26.Mos.HIV with high-dose clade C gp140 elicited similar immune responses, with 67% complete protection and 94% per-exposure protection against six consecutive challenges with simian-human immunodeficiency virus. The Ad26.Mos.HIV–clade C gp140 regimen was compared with tetravalent Ad26.Mos4.HIV (encoding two mosaic Env antigens and two mosaic Gag–Pol antigens) with clade C gp140 in the phase 1–2a study TRAVERSE (HVTN 117/HPX2004), with Ad26.Mos4.HIV–clade C gp140 achieving a superior immune response. In ASCENT (HVTN 118/HPX2003), a phase 1–2a study assessing tetravalent vaccines Ad26.Mos4.HIV–clade C gp140 and Ad26.Mos4.HIV–clade C gp140–mosaic gp140, greater immune responses were observed with the regimen incorporating mosaic gp140.

Added value of this study

Imbokodo (HVTN 705/HPX2008) was a proof-of-concept study assessing the efficacy and safety of a heterologous tetravalent mosaic Ad26 (Ad26.Mos4.HIV) and aluminium phosphate-adjuvanted clade C gp140 vaccine regimen in young women (aged 18–35 years) at risk of HIV-1 in southern Africa. The vaccine

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regimen was safe and well tolerated but did not show efficacy in preventing HIV-1 acquisition. High rates of HIV-1 acquisition were seen in participants, highlighting the need to continue to fund biomedical interventions to prevent HIV-1 acquisition. Clinical trials are central to advancing the field of HIV-1 vaccine research, yet this study is one of a small minority assessing vaccine efficacy. Moreover, the negative finding for vaccine efficacy in this study highlights the limitations inherent to the current experimental animal challenge model. Importantly, the Imbokodo programme exhibited principles of equity and inclusivity in its conduct by supporting full HIV-1 prevention services before and during the study, by engaging community stakeholders, and by recruiting participants from a group at high risk that is under-represented in HIV-1 research. Imbokodo could thus serve as an ethical model for future HIV-1 research.

Implications of all the available evidence

Despite nearly 40 years of research aiming to develop an effective vaccine against HIV-1, this development has proven to be an extremely complex and challenging task, and no vaccine candidate has elicited potent and durable protective efficacy. Although the Ad26.Mos4.HIV and clade C gp140 vaccine has been shown to induce protection in non-human primates, these observations did not translate to preventive efficacy in the Imbokodo trial. Similarly, the Ad26.Mos4.HIV–clade C gp140–mosaic gp140 vaccine regimen evaluated in the phase 3 Mosaico (NCT03964415) study also did not show efficacy against acquiring HIV-1 in men who have sex with men and transgender individuals. Novel strategies for HIV-1 vaccine development are needed, including a more relevant animal model. Most HIV-1 vaccine trials have elicited non-neutralising responses, and approaches employing broadly neutralising antibodies (either vaccine-induced or administered by passive immunisation) might be needed to achieve goals of protection against HIV-1.

A multivalent HIV-1 vaccine regimen based on a replication-incompetent adenovirus 26 (Ad26) vector was developed through a mosaic immunogen approach to elicit broad cellular and humoral cross-clade responses against diverse HIV-1 variants.[3–5] The addition of adjuvanted recombinant clade C glycoprotein (gp) 140 to an Ad26-based mosaic vaccine expressing Env, Gag, and Pol antigens (Ad26.Mos.HIV) provided 94% per-exposure protection and 67% complete protection against six consecutive rectal simian-human immunodeficiency virus (SHIV-SF162P3) challenges in non-human primates and induced immune response levels in humans that were associated with protection in non-human primate challenge studies.[6] Although not evaluated in non-human primates, adding an additional Ad26 vector encoding a second complementary mosaic Env antigen (to create the Ad26.Mos4.HIV vaccine) substantially increased the breadth and magnitude of participants' immune responses against diverse HIV-1 strains in a phase 1–2a study.[4]

Imbokodo (HVTN 705/HPX2008) was a proof-of-concept study to evaluate the protective efficacy and safety of a mosaic-based HIV-1 vaccine regimen in young women at risk of HIV-1 in southern Africa.

Methods

Study design and participants

This multicentre, randomised, double-blind, placebo-controlled, phase 2b study was conducted at 23 clinical trial sites in Malawi, Mozambique, South Africa, Zambia, and Zimbabwe. Eligible participants were healthy women (assigned female sex at birth) aged 18–35 years who had had sexual intercourse with a male partner two or more times in the 30 days before screening, were at increased risk of acquiring HIV-1, and were HIV-1-negative and HIV-2-negative. Participants agreed to consistently use effective contraception from at least 21 days before enrolment to 3 months after their last vaccination. The full inclusion and exclusion criteria are listed in the protocol (appendix pp 79–82).

The study design consisted of two stages: stage 1 was defined as the period from trial start until the last enrolled participant's month 24 visit and stage 2 as the period from the last enrolled participant's month 24 visit until their month 36 visit. Participants were followed up for acquisition of HIV-1 for 2 or more years after enrolment until the primary analysis was conducted after the last participant's month 24 visit (ie, the end of stage 1). The use of oral PrEP (tenofovir disoproxil fumarate–emtricitabine) was offered either directly or at an affiliated facility proximal to the study site. Details on study design and oversight are provided in the appendix (p 2). The last participant's final visit occurred on Feb 2, 2022; data are presented from the database lock on April 29, 2022.

This study adheres to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol, protocol amendments, and other relevant documents were approved by institutional review boards, ethics committees, and the applicable regulatory entities. All participants provided written informed consent. An independent data and safety monitoring board periodically reviewed the safety and efficacy data. This study is registered with ClinicalTrials.gov, NCT03060629.

Randomisation and masking

Participants were centrally randomly assigned (1:1) to receive the Ad26.Mos4.HIV and clade C gp140 vaccine regimen or placebo in stratified permuted blocks via an interactive web response system. The randomisation

sequence was obtained through computer-generated random numbers under provision of the sponsor and was provided to each clinical trial site. Before a participant could be randomly assigned, all eligibility criteria for that participant must have been reviewed by at least two clinical research site staff members. When review of the criteria was complete and if the participant met all the eligibility requirements, clinical research site staff could request randomisation. Clinical research site staff were involved later in the study.

At each site, the pharmacist with primary responsibility for dispensing study vaccines was charged with maintaining security of the treatment assignments. Study participants, study site personnel (except those with primary responsibility for study vaccine preparation and dispensing), and investigators remained masked to treatment group allocation throughout the study. An overlay was placed on all vaccination syringes to preserve blinding.

Procedures

At months 0, 3, 6, and 12, participants received Ad26.Mos4.HIV or saline placebo via intramuscular injection. At months 6 and 12, participants also received adjuvanted clade C gp140 or placebo via injection. Additional details on the study vaccinations are provided in the appendix (p 2).

The monitoring period for solicited local and systemic adverse events (AEs) was 3 days (for 20 of the sites) or 7 days (for three of the sites) after each injection. For unsolicited AEs, the monitoring period was 30 days after each vaccination visit. For serious AEs, AEs of special interest, and AEs leading to early withdrawal from the study or discontinuation of study vaccine administration, the monitoring period was for the study duration. Participants were assessed for HIV-1 or HIV-2 acquisition at months 0, 3, 6, 7, 9, and every 3 months thereafter; additional details are in the appendix (p 2). Participants were counselled about risk of HIV-1 at each visit. Regular testing and treatment or appropriate referrals for sexually transmitted infections (STIs) were provided. To assess the potential effect of PrEP or post-exposure prophylaxis (PEP) on endpoint accrual, dried blood spot samples were collected for quantitative assessment of intracellular tenofovir diphosphate (TFV-DP) concentrations (further described in the appendix [p 3]). The presence of adenovirus vector neutralising antibodies at baseline was measured with an Ad26 virus neutralisation assay as previously described.[5]

Outcomes

The primary efficacy endpoint was vaccine efficacy in preventing confirmed HIV-1 acquisition diagnosed between the month 7 and month 24 visits after the first vaccination (VE[7–24]) in the per-protocol cohort. HIV testing was performed at a central laboratory in South Africa. Secondary endpoints reported within this Article included VE(7–24) in the modified intention-to-treat (MITT) cohort, vaccine efficacy from months 0–24 (VE[0–24]) in the MITT cohort, and vaccine efficacy from months 13–24 (VE[13–24]) in the full immunisation set and MITT cohorts. The VE(7–24) and VE(0–24) endpoints included time before completion of the full vaccine regimen at 12 months (see figure 1 for an overview of each efficacy endpoint in relation to vaccine administration). Prespecified analyses of vaccine efficacy by demographic and other baseline characteristics were also conducted. Vaccine efficacy from month 0 or month 12 until month 36 were to be assessed only if stage 2 occurred (which it did not). Other secondary endpoints included immune responses following the third and fourth vaccinations, evaluation of immunogenicity and immune response biomarkers among vaccine recipients after the third vaccination (to identify potential correlates of risk and vaccine efficacy), viral sequences from participants who acquired HIV-1 at the earliest possible post-acquisition timepoint and subsequent visits, and genotypic characteristics of viral sequences from participants who had acquired HIV-1 from month 7 to month 24; data for these endpoints are to be reported separately. All of the secondary endpoints are listed and described in the protocol (appendix pp 59–61). The primary safety endpoints, analysed in the full analysis set based on the actual injection received (vaccine or placebo; full analysis set [actual study injection]), were the incidences of unsolicited AEs, solicited local and systemic AEs, serious AEs, AEs of special interest (including but not limited to potential immune-mediated diseases; a full list is provided in the protocol [appendix p 162]), and AEs leading to participant withdrawal or discontinuation of the study vaccine.

Statistical analysis

A sample size of 2600 was estimated to provide 90% power to reject a null hypothesis of VE(7–24) being 0% or less under an assumed VE(7–24) of 50% on the basis of a one-sided 0·025-level Wald test. Additional details are provided in the appendix (p 3).

Analyses were conducted in the following populations: the full analysis set, which included all randomly assigned participants who received one study injection or more; the MITT cohort, which included participants in the full analysis set who were HIV-1-negative at the first vaccination visit; the per-protocol cohort, which included participants in the full analysis set who were HIV-1-negative 4 weeks after the third vaccination, received all planned vaccinations at the first three vaccination visits within the protocol-specified windows, and had no major protocol deviations that could affect vaccine efficacy; and the full immunisation set, which included participants in the full analysis set who were HIV-1-negative 4 weeks after the fourth vaccination and had received all planned injections within the respective visit windows.

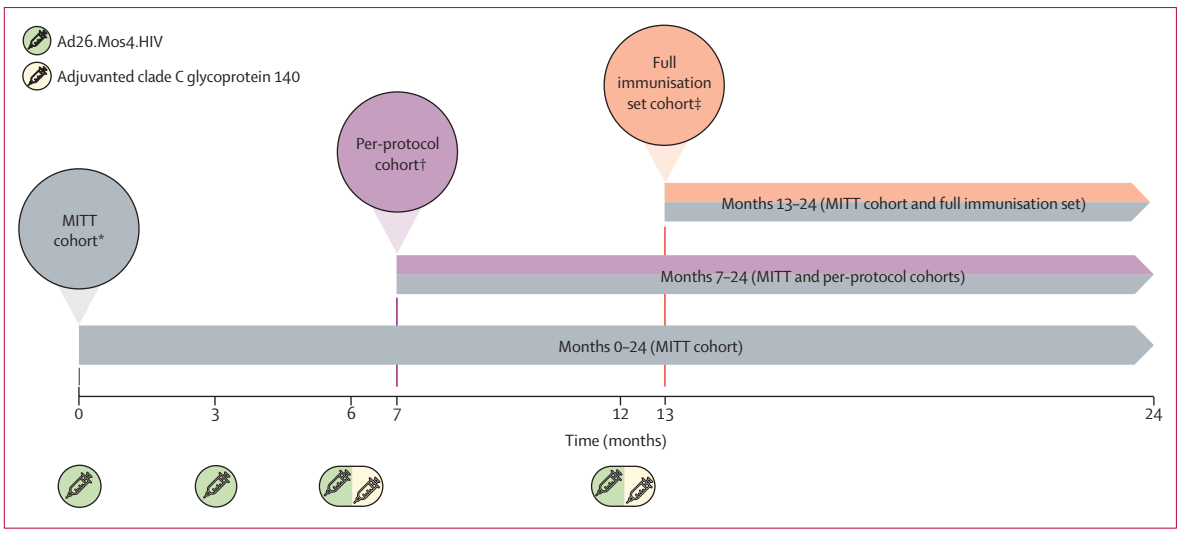


Figure 1: **Vaccination schedule and study periods among key populations**
The study vaccination schedule is shown below the timeline. Arrow bars indicate each time period evaluated in efficacy assessments, with the relevant population(s) in parentheses. Circular callouts with cohort names represent the study month at which each population was to have confirmation of being HIV-1-negative. Ad26.Mos4.HIV=an Ad26-based mosaic vaccine expressing Env, Gag, and Pol antigens. HIV-1=HIV type 1. MITT=modified intention-to-treat. *The MITT cohort included participants in the full analysis set who were HIV-1-negative at the first vaccination visit. †The per-protocol cohort included participants in the full analysis set who were HIV-1-negative 4 weeks after the third vaccination, received all planned vaccinations at the first three vaccination visits within the protocol-specified windows, and had no major protocol deviations that could affect vaccine efficacy. ‡The full immunisation set included participants in the full analysis set who were HIV-1-negative 4 weeks after the fourth vaccination and had received all planned injections within the respective visit windows.

Ad26 vector immunogenicity analyses were performed in the case–control cohort, which included case participants (individuals with no evidence of HIV-1 acquisition before or at the month 7 visit but with HIV-1 acquisition diagnosed after the month 7 visit and before or at the month 24 visit) and control participants (individuals who remained HIV-1-negative until the month 27 visit) selected from the per-protocol cohort. All case participants in the vaccine group and five case participants in the placebo group, randomly selected from all eligible placebo case participants, were included in the case–control cohort. Control participants were randomly sampled in a 5:1 (control participant:case participant) ratio in the vaccine group and in a 1:1 (control participant:case participant) ratio in the placebo group from all eligible control participants in the vaccine and placebo groups. Control participants were frequency-matched to case participants on the basis of treatment (vaccine *vs* placebo), BMI (<25 kg/m² *vs* ≥25 to <30 kg/m² *vs* ≥30 kg/m²), and region (South Africa *vs* not South Africa).

The primary analysis of VE(7–24) was defined as one minus the cumulative incidence ratio (vaccine to placebo) of the HIV-1 endpoint between month 7 and month 24. Due to the use of visit windows, many month 24 visits occurred slightly more than 24 months after enrolment; therefore, VE(7–24) was reported until 25·91 months post enrolment. VE(7–24) was estimated with the transformed Nelson–Aalen estimator for the cumulative hazard function at month 25·91 and reported with a two-sided 95% log-cumulative hazard-based Wald CI without adjustment for interim monitoring. If the lower bound of the two-sided 95% CI for VE(7–24) was more than 0%, masked follow-up would continue until stage 2. Otherwise, participants would be unmasked at the end of stage 1, and stage 2 would not occur. Secondary vaccine efficacy analyses were assessed with the same methods as for the primary endpoint. For the assessment of baseline Ad26 immunogenicity, weighted response rates, medians, and quartiles were calculated with inverse probability of sampling weights to account for the two-phase sampling design; estimates and inferences are reported for the population of eligible participants from which the case–control cohort was selected. Additional details are provided in the appendix (pp 3, 4, 164).

Role of the funding source

The HIV Vaccine Trials Network and Janssen, in collaboration with the Bill & Melinda Gates Foundation and Ragon Institute, had roles in the study design. The HIV Vaccine Trials Network, Janssen, and the Ragon Institute had roles in the collection, analysis, and interpretation of data; the writing of this Article; and the decision to submit for publication.

Results

Between Nov 3, 2017, and June 30, 2019, 2654 women were randomly assigned, of whom 2636 were enrolled and received at least one injection. The full analysis set (assigned study injection) included 1313 participants assigned to the Ad26.Mos4.HIV and clade C gp140

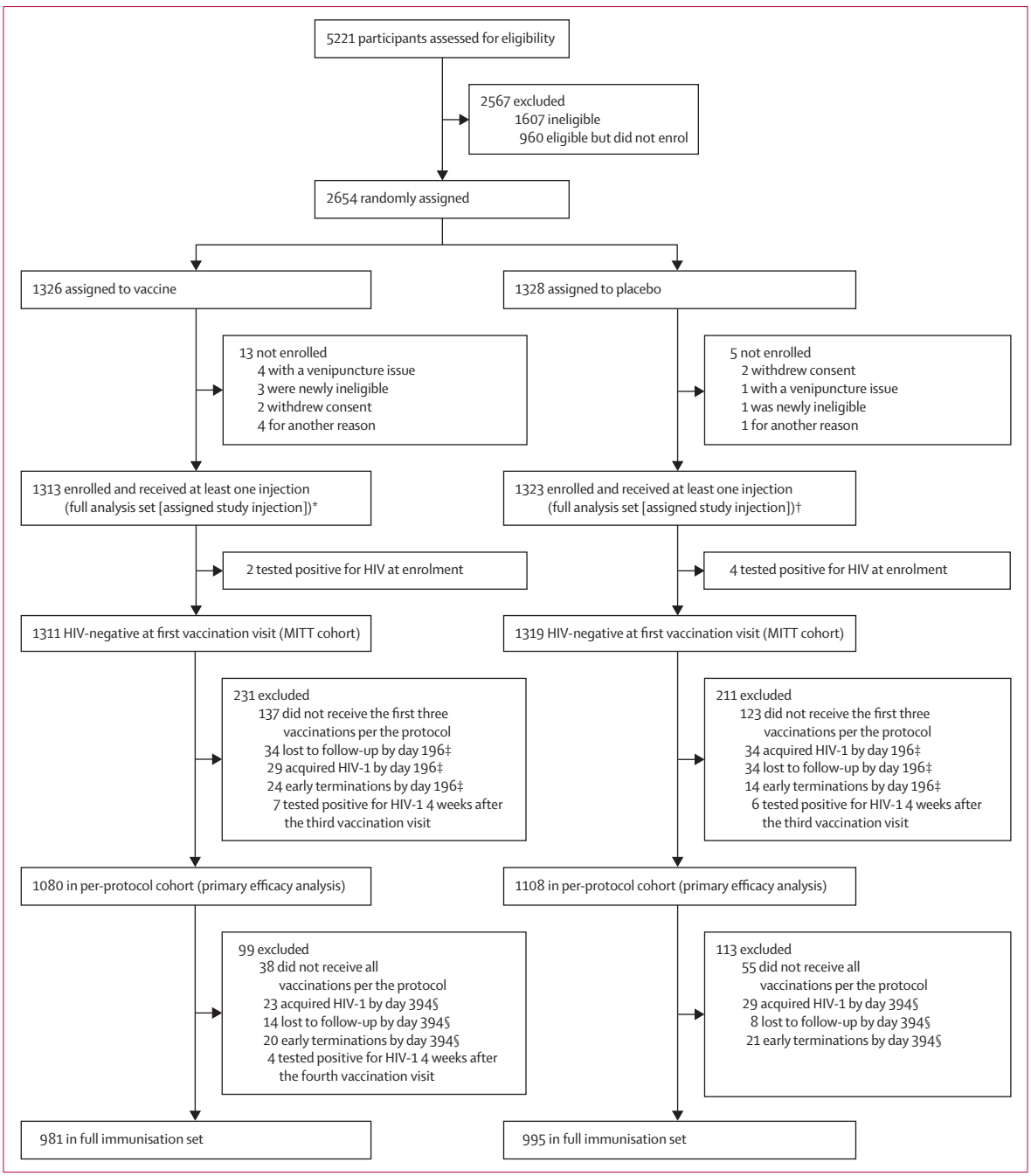


Figure 2: **Trial profile**
HIV-1=HIV type 1. MITT=modified intention-to-treat. *The full analysis set by actual study injection received (vaccine; full analysis set [actual study injection]) included 1317 participants. †The full analysis set by actual study injection received (placebo; full analysis set [actual study injection]) included 1319 participants. ‡Day 196 marked the end of the window for visit 6. §Day 394 marked the end of the window for visit 9.

vaccine regimen and 1323 to placebo. Two participants who received the vaccine and four who received placebo were subsequently found to be HIV-positive at enrolment; hence, the MITT cohort included 1311 women who received the vaccine and 1319 who received placebo (figure 2). Several participants did not receive the study injection to which they were assigned. Safety analyses were conducted in the full analysis set (actual study injection), which included 1317 participants who received the study vaccine and 1319 participants who received placebo; participants who received one vaccination or more with the study vaccine were assigned to the vaccine group. The per-protocol cohort included 1080 women in the vaccine group and 1108 women in the placebo group;

the full immunisation set included 981 women in the vaccine group and 995 women in the placebo group. Overall, 1213 (92·4%) of 1313 participants in the vaccine group and 1228 (92·8%) of 1323 participants in the placebo group completed all study vaccinations (appendix p 10). Major protocol deviations were reported for 357 (13·5%) of 2636 participants (appendix p 11).

At baseline, the median age was 23 years (IQR 20–25), 1201 (45·6%) of 2636 participants reported exchanging sex for money or gifts, and 844 (32·0%) of 2636 participants had a positive STI test result (table 1). Demographic and risk characteristics were similar between the study groups.

The prespecified criteria to demonstrate vaccine efficacy were not met. Over month 7 to month 24 after the first vaccination in the per-protocol cohort, there were 54 HIV-1 acquisitions among the 1080 participants in the vaccine group and 65 acquisitions among the 1108 participants in the placebo group, with an estimated incidence rate of 3·38 acquisitions (95% CI 2·54–4·41) per 100 person-years in the vaccine group and 3·94 acquisitions (3·04–5·03) per 100 person-years in the placebo group, and an estimated VE(7–24) of 14·10% (95% CI –22·00 to 39·51; p=0·40; figure 3A, B; appendix p 12). Secondary analyses of VE(7–24), VE(0–24), and VE(13–24) in the MITT cohort and VE(13–24) in the full immunisation set also showed that vaccine efficacy did not differ significantly from 0% (figure 3B, C). Subgroup analyses of VE by age, BMI, and country of enrolment revealed no notable differences from the main efficacy populations (appendix p 13). After discussing the results of the primary analysis with the data and safety monitoring board and the study oversight group, the sponsor decided not to proceed to stage 2.

Of the 3467 dried blood spot samples assayed from 1797 participants, detectable TFV-DP concentrations were found in 61 (3·6%) of 1696 samples from the vaccine group and 46 (2·6%) of 1771 samples from the placebo group, and effective TFV-DP concentrations were found in seven (0·4%) of 1696 samples from the vaccine group and six (0·3%) of 1771 samples from the control group (appendix p 14). The estimated percentage of person-years at risk on effective PrEP or PEP was 0·4% for both groups. PrEP or PEP use varied across sites, with the proportion of samples with detectable TFV-DP concentrations ranging from three (5·5%) of 55 samples to 32 (14·7%) of 218 samples at four sites in South Africa and Zimbabwe; one (0·6%) of 166 samples to two (4·3%) of 47 samples at 13 sites in South Africa, Zambia, and Zimbabwe; and 0 of 619 samples at the remaining six sites in Malawi, Mozambique, South Africa, and Zambia.

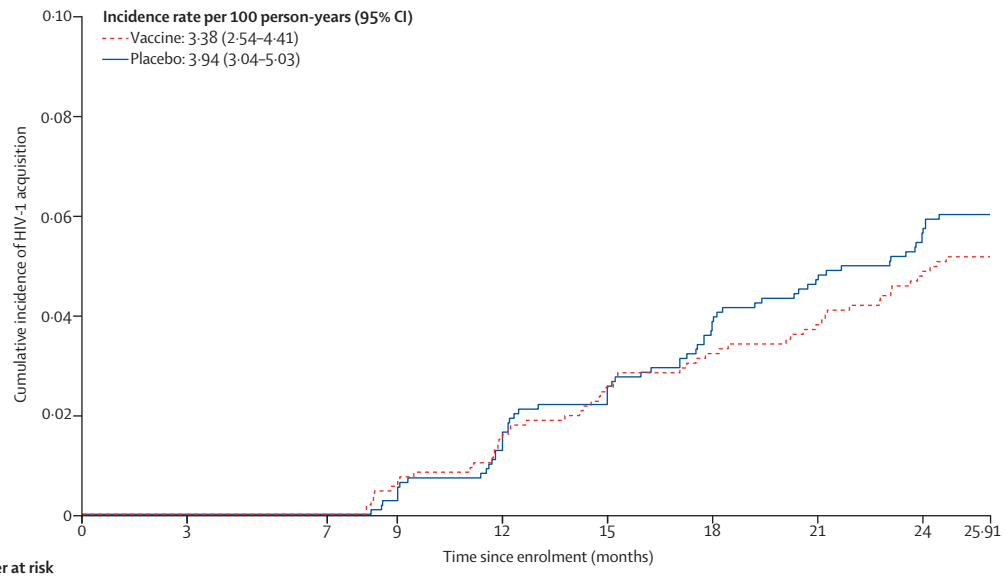
In the full analysis set (actual study injection), 939 (71·3%) of 1317 participants in the vaccine group and 915 (69·4%) of 1319 participants in the placebo group had one or more unsolicited grade 2 or higher AEs (table 2). None of the serious unsolicited AEs (in 49 [3·7%] of 1317 participants in the vaccine group and 37 [2·8%] of 1319 participants the placebo group) were related to the study intervention. Grade 2 related unsolicited AEs occurred in three (0·2%) of 1317 participants in the vaccine group (headache, cellulitis at the injection site, and pruritus) and four (0·3%) of 1319 participants in the placebo group (eye pain, macular rash, pruritus, and rash). Grade 3 related unsolicited AEs (hypersensitivity

	Vaccine (n=1313)	Placebo (n=1323)
Age, years	22 (20–25)	23 (21–25)
Age range		
18–20 years	346 (26·4%)	330 (24·9%)
21–30 years	879 (66·9%)	909 (68·7%)
31–35 years	88 (6·7%)	84 (6·3%)
Country		
Malawi	78 (5·9%)	79 (6·0%)
Mozambique	23 (1·8%)	22 (1·7%)
South Africa	882 (67·2%)	892 (67·4%)
Zambia	164 (12·5%)	165 (12·5%)
Zimbabwe	166 (12·6%)	165 (12·5%)
BMI		
<18·5 kg/m²	64 (4·9%)	78 (5·9%)
18·5 to <25 kg/m²	606 (46·2%)	598 (45·2%)
≥25 kg/m²	643 (49·0%)	647 (48·9%)
Number of sex partners during previous month*		
0	4 (0·3%)	4 (0·3%)
1	561 (42·7%)	542 (41·0%)
2	295 (22·5%)	312 (23·6%)
3–4	217 (16·5%)	206 (15·6%)
≥5	236 (18·0%)	259 (19·6%)
Condom use*		
Always	147 (11·2%)	158 (11·9%)
Sometimes	927 (70·6%)	946 (71·5%)
Never	239 (18·2%)	219 (16·6%)
Risk-related behaviours during the previous month*		
Oldest partner aged >26 years	916 (69·8%)	960 (72·6%)
Exchange of sex for money or gifts	590 (44·9%)	611 (46·2)
Spouse or main partner has other partners	379 (28·9%)	402 (30·4%)
Living with main partner†	177 (13·5%)	187 (14·1%)
Unprotected sex with HIV-positive partner	12 (0·9%)	13 (1·0%)
Positive for any STI‡	423 (32·2%)	421 (31·8%)
Positive for *Chlamydia trachomatis*§¶	268 (20·4%)	282 (21·3%)

Data are median (IQR) or n (%). Percentages might not total 100% due to rounding. STI=sexually transmitted infection. *Self-reported risk-related behaviours. †The behaviour associated with more risk is not living with the participant's main partner. ‡Indicates positivity for any of the STIs for which a participant was tested: syphilis, *Trichomonas vaginalis*, *Neisseria gonorrhoea*, and *Chlamydia trachomatis*. §Test performed on cervical or vaginal swab or urine; result was positive if either test was positive. ¶*Chlamydia trachomatis* was the most common STI among the tested participants.

Table 1: **Baseline participant demographic, risk, and clinical characteristics (full analysis set [assigned study injection])**

A



Number at risk (number censored)										
Vaccine	1080	1080	1067	1056	1039	1019	1002	991	975	972
	(0)	(0)	(13)	(18)	(26)	(34)	(44)	(49)	(54)	(1026)
Placebo	1108	1108	1099	1091	1071	1052	1034	1019	1008	1004
	(0)	(0)	(9)	(14)	(24)	(28)	(32)	(38)	(39)	(1043)
Cumulative HIV-1 acquisitions										
Vaccine	0	0	0	6	17	27	34	40	51	54
Placebo	0	0	0	3	18	28	42	51	62	65

B

	Vaccine (n=1313)				Placebo (n=1323)			
	Participants evaluated	HIV-1 acquisitions	Total person-years of follow-up*	Incidence rate per 100 person-years, % (95% CI)	Participants evaluated	HIV-1 acquisitions	Total person-years of follow-up*	Incidence rate per 100 person-years, % (95% CI)
Primary efficacy								
Per-protocol cohort (months 7–24)	1080	54	1598	3·38 (2·54–4·41)	1108	65	1648	3·94 (3·04–5·03)
Secondary efficacy								
MITT cohort (months 7–24)	1214	61	1791	3·41 (2·60–4·37)	1232	67	1828	3·67 (2·84–4·66)
MITT cohort (months 0–24)	1311	91	2522	3·61 (2·90–4·43)	1319	102	2569	3·97 (3·24–4·82)
MITT cohort (months 13–24)	1152	37	1203	3·08 (2·17–4·24)	1167	36	1226	2·94 (2·06–4·06)
Full immunisation set (months 13–24)	981	32	1027	3·11 (2·13–4·40)	995	35	1047	3·34 (2·33–4·65)

C

	Cumulative HIV-1 acquisitions				Vaccine efficacy point estimate, % (95% CI)†	p value‡
	n	Total	Vaccine	Placebo		
Per-protocol cohort						
VE(7–24)	2188	119	54	65	14·10 (–22·00 to 39·51)	0·40
MITT cohort						
VE(7–24)	2446	128	61	67	7·01 (–30·31 to 33·65)	0·67
VE(0–24)	2630	193	91	102	8·78 (–19·68 to 30·48)	0·51
VE(13–24)	2319	73	37	36	–4·65 (–64·38 to 33·37)	0·84
Full immunisation set						
VE(13–24)	1976	67	32	35	6·82 (–49·26 to 41·83)	0·77

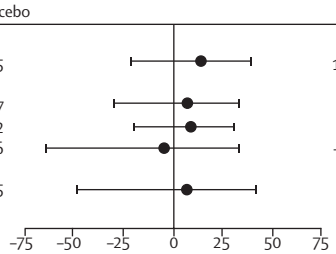


Figure 3: **Vaccine efficacy**

(A) Cumulative incidence of HIV-1 acquisition over 7–24 months (per-protocol cohort). (B) Incidence of HIV-1 acquisition in the primary and secondary analysis cohorts. (C) Point estimates of vaccine efficacy in the cohorts analysed for primary (per-protocol cohort) and secondary (MITT cohort and full immunisation set) endpoints. HIV-1=HIV type 1. MITT=modified intention-to-treat. VE(7–24)=vaccine efficacy in preventing confirmed HIV-1 acquisition diagnosed between the month 7 and month 24 visits after the first vaccination. VE(0–24)=vaccine efficacy from months 0–24. VE(13–24)=vaccine efficacy from months 13–24. *Until 25·91 months, which is the right edge of the allowable month 24 visit window. †Censored at 25·91 months, which is the right edge of the allowable month 24 visit window. ‡Two-sided α=0·05 level Wald-based hypothesis tests evaluating the equality of the log-cumulative hazard functions at the cutoff time (25·91 months).

and urticaria) occurred in one (0·1%) of 1319 participants in the placebo group. Unrelated fatal AEs occurred in six (0·5%) of 1317 participants in the vaccine group and four (0·3%) of 1319 participants in the placebo group. AEs of special interest were reported in two (0·2%) of 1317 participants in the vaccine group (moderate toxic nodular goitre and severe type 1 diabetes) and three (0·2%) of 1319 participants in the placebo group (moderate lichen planus and two cases of severe type 1 diabetes); all were unrelated to study vaccination. No cases of thrombosis with thrombocytopenia syndrome were observed. 61 pregnancies occurred during the period in which pregnancy was proscribed per protocol (21 days before enrolment until 3 months after the last vaccination); pregnancy outcomes are summarised in the appendix (p 15). Three (0·2%) of the 1317 participants in the vaccine group and three (0·2%) of the 1319 participants in the placebo group discontinued vaccination due to unsolicited AEs (idiopathic intracranial hypertension [unrelated], fatal stab wound [unrelated], and pruritus [related] in the vaccine group and hypersensitivity, rash, and macular rash [all related] in the placebo group).

Solicited local AEs of pain or tenderness, erythema, and induration or swelling occurred more frequently with the vaccine than placebo (figure 4A). More participants in the vaccine group reported solicited local AEs after the first vaccination than after the three subsequent vaccinations; in the placebo group, the frequency was similar after all four vaccinations (appendix p 5). Most solicited local AEs were grade 1 or grade 2. In the vaccine group, 50·3% (663) of 1317 participants had grade 1 or 2 solicited local AEs and 0·8% (ten) of 1317 participants had grade 3 or 4 solicited local AEs. In the placebo group, 23·1% (305) of 1319 participants had grade 1 or 2 solicited local AEs and 0·2% (three) of 1319 participants had grade 3 or 4 solicited local AEs.

Solicited systemic AEs, of which headache was the most common, were more frequent after the vaccine than placebo (figure 4B). More participants in both the vaccine and placebo groups reported solicited systemic AEs after the first vaccination than after the other vaccinations (appendix p 7). Most solicited systemic AEs were grade 1 or grade 2 after any vaccination; the percentage of participants with grade 1 or grade 2 and grade 3 or 4 solicited systemic AEs was 65·5% (863 of 1317) and 2·6% (34 of 1317), respectively, in the vaccine group and 57·8% (763 of 1319) and 1·5% (20 of 1319), respectively, in the placebo group. Overall, three (0·2%) of 1317 participants in the vaccine group (two participants with pyrexia and one participant with erythema or redness) and one (0·1%) of 1319 participants in the placebo group (with pyrexia) discontinued vaccination due to a solicited AE.

Among participants with an available Ad26 titre in the case–control cohort, baseline seropositivity for Ad26 neutralising antibodies was observed in 45 (83·3%) of 54 case participants and 230 (85·5%) of 269 control participants in the vaccine group and in all participants in the placebo group (five of five case participants and five of five control participants; appendix p 16). Baseline Ad26 titres ranged substantially between participants; however, median Ad26 response was similar between case participants and control participants in the vaccine group, with a median Ad26 neutralisation titre 90% inhibitory concentration of 203·5 (IQR 114·0–506·3) for case participants and 220·0 (81·1–574·0) for control participants.

	Vaccine (n=1317)	Placebo (n=1319)
Unsolicited AEs	980 (74·4%)	961 (72·9%)
Grade 1	41 (3·1%)	46 (3·5%)
Grade 2	882 (67·0%)	869 (65·9%)
Grade 3	44 (3·3%)	39 (3·0%)
Grade 4	7 (0·5%)	3 (0·2%)
Grade 5 (fatal)	6 (0·5%)*	4 (0·3%)†
Serious AE	49 (3·7%)	37 (2·8%)
Unsolicited AEs related to vaccine or placebo	12 (0·9%)	11 (0·8%)
Grade 1	9 (0·7%)	6 (0·5%)
Grade 2	3 (0·2%)	4 (0·3%)
Grade 3	0	1 (0·1%)

Data are n (%). Participants who received one vaccination or more with the study vaccine were assigned to the vaccine group. AE=adverse event. *Fatal AEs in the vaccine group were abdominal mass, alcoholic psychosis, anaemia, headache, respiratory tract infection, and stab wound (anaemia and respiratory tract infection occurred in the same participant). Additionally, an offspring of a participant in the vaccine group died on the day of birth, and the AE was reported as congenital anomaly in the offspring. †Fatal AEs in the placebo group were death (cause unknown), gunshot wound, maternal death during childbirth, and pneumonia.

Table 2: **Unsolicited AEs (full analysis set [actual study injection])**

Discussion

In this proof-of-concept study, a heterologous vaccine regimen of Ad26.Mos4.HIV and aluminium phosphate-adjuvanted clade C gp140 protein did not show efficacy in preventing HIV-1 in southern African women aged 18–35 years at risk of acquiring HIV-1. There were no safety concerns; the study was ended after stage 1 due to the absence of efficacy.

Although this vaccine regimen was shown in phase 1–2a trials[4,5] to solicit high levels of binding and functional antibody and T-cell responses, which were associated with protection against a series of SHIV-SF162P3 challenges in non-human primates, these immune responses did not translate to preventive efficacy in the Imbokodo trial. The mechanisms accounting for this absence of efficacy could include: very high rates of HIV-1 exposure in the at-risk study population, which could have overwhelmed any protective effect of vaccination; genetic diversity of circulating clade C viruses at study sites that might be too

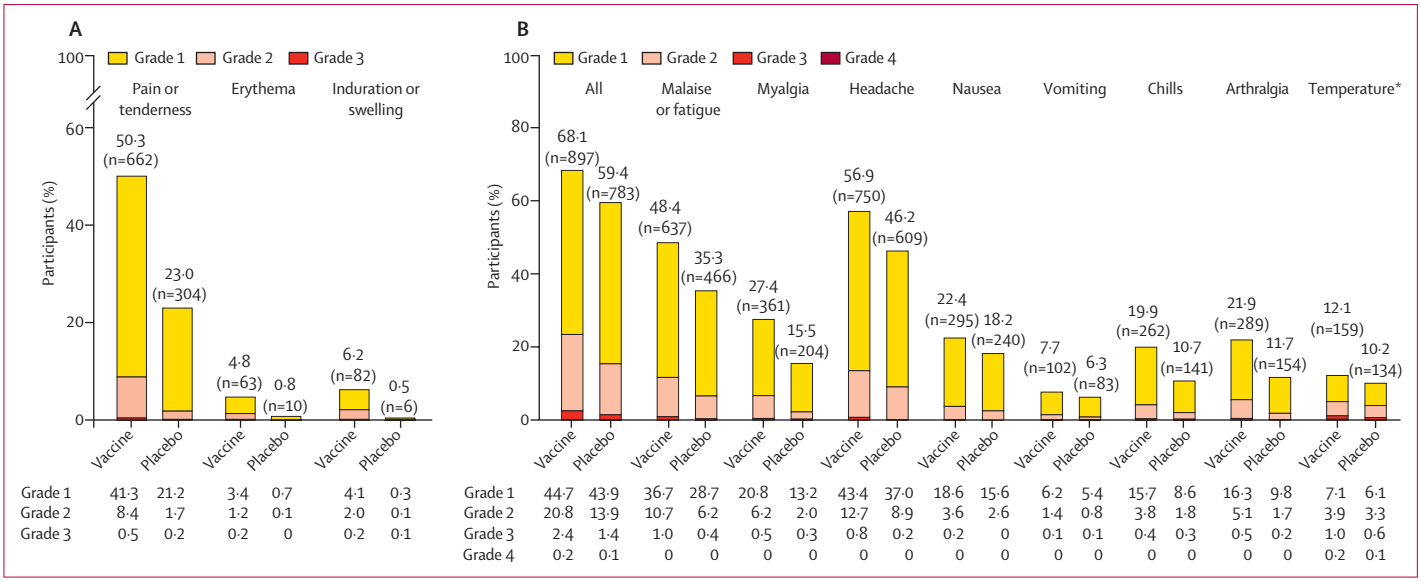


Figure 4: **Solicited AEs (full analysis set [actual study injection])***

Solicited AEs overall (ie, including all injections) assessed among 1317 participants in the vaccine group and 1319 participants in the placebo group. Data are solicited local (A) and systemic (B) AEs reported within 3 days or 7 days after injection, depending on the study site. Participants were monitored for solicited local and systemic AEs for 3 days post injection at 20 sites and for 7 days post injection at three sites. AE=adverse event. *Three participants (two participants in the vaccine group and one participant in the placebo group) each had a grade 4 temperature event (defined as a temperature ≥40°C).

distant from the vaccine-induced specificities; concomitant STIs or sexual intercourse mucosal traumas in study participants that increased their susceptibility; or insufficient levels of as-yet-unidentified adaptive or innate immune responses required for reducing HIV-1 acquisition. Moreover, Moodie and colleagues[7] showed that the efficacy identified with one HIV-1 vaccine might not be generalisable to other regimens, clades, or study populations. Thus, although this vaccine regimen provided more than 90% per-exposure protection in non-human primate challenge studies,[6] the SHIV-SF162P3–rhesus monkey preclinical challenge model was not predictive of vaccine efficacy in humans in this trial. This finding might reflect the underlying limitations of the non-human primate model (including the use of a SHIV that does not mimic the breadth of circulating viruses, different transmission modes [eg, intrarectal transmission], species differences in immune functions, low numbers of exposures, low diversity in the challenge virus, time between completion of vaccination and first challenge, the absence of local trauma and force of exposure effects, and the absence of rectal co-infections) that might limit applicability of the current experimental challenge model to human studies.[8] More relevant models need to be established for future assessments.

The absence of efficacy observed in the Imbokodo (HVTN 705/HPX2008) trial echoes that observed in another HIV-1 vaccine study, the Uhambo (HVTN 702) trial.[9] On the basis of cellular and humoral responses and a 31% efficacy obtained with a canarypox-vectored HIV-1 vaccine and a gp120 boost in the RV144 study in Thailand (a low-to-moderate HIV-1 risk setting),[10] a clade C-adapted regimen was tested in participants at increased risk of HIV in South Africa, but the vaccine was not efficacious in this population.[9] The Imbokodo trial was conducted in a similar period and geographical location to the Uhambo trial (with 67% of Imbokodo participants in South Africa). Although vaccine vectors, vector-encoded immunogens, vaccine proteins, and adjuvants differed between the Uhambo and Imbokodo trials, both regimens have been shown to induce functional but non-neutralising HIV-1-specific antibodies.[4,5,9,11] In phase 1–2a studies of both regimens, neutralising antibodies were generated against laboratory-adapted viruses but not against circulating viruses, even at a low titre.[5,11] Although no overall efficacy was shown, immune correlates of HIV-1 risk that involved cellular and humoral responses working together were reported in both the Uhambo trial[7] and the phase 2b HVTN 505 trial.[12]

Also similar between the Uhambo and Imbokodo trial results were the low amount of PrEP use among participants (with effective TFV-DP concentrations in <1% of dried blood spot samples in the Imbokodo trial) and the rate of HIV-1 acquisition among participants who received placebo (4·2 acquisitions per 100 person-years in Uhambo *vs* 3·9 acquisitions per 100 person-years in Imbokodo).[9] This incidence was approximately 14 times higher than that observed among women in the earlier RV144 study[9] and might have contributed to the absence of statistically significant protection observed in the Uhambo and Imbokodo trials. To that point, vaccine efficacy in the RV144 trial was also lower in participants at higher risk of HIV-1 acquisition.[10]

In this study, high levels of baseline Ad26 seropositivity were observed, with similar response rates seen across active and control participants, indicating no effect of Ad26 baseline seropositivity on HIV-1 acquisition. The seropositivity frequencies were in line with our findings from a previous phase 1–2a trial, in which we detected pre-existing, naturally occurring Ad26 neutralising antibodies in 89% of participants from east Africa compared with only 5% of participants from the USA.[5]

The Imbokodo vaccine regimen was safe and well tolerated with no vaccine-related serious AEs. The solicited local and systemic AE profiles were generally consistent with those in the phase 1–2a studies TRAVERSE[4] and ASCENT.[5] Repeated doses of the Ad26-based vaccine did not result in increased frequency or severity of local and systemic AEs. No cases of thrombocytopenia syndrome or vaccine-induced immune thrombotic thrombocytopenia, previously rarely reported with another Ad26-vectored vaccine against severe acute respiratory syndrome coronavirus 2,[13] were observed, although the odds of detecting these very rare events in the vaccine group (n=1317) were small. No cases of thrombocytopenia syndrome have been observed in the overall Janssen HIV-1 vaccine programme to date.

The Imbokodo protocol specified high standards of HIV prevention practice, including evidence-based behavioural risk-reduction counselling,[14] and, when indicated, available, or appropriate, advocacy and referral of participants' partners for medical male circumcision, provision of free condoms and lubricant, regular testing and treatment or referral for HIV and other STIs, counselling and referral for PEP, and access to PrEP through all study sites. Nevertheless, low rates of PrEP and PEP use were observed, consistent with other studies showing low PrEP uptake, adherence, and persistence in women in sub-Saharan Africa.[15–17]

The efficacy of a similar heterologous HIV-1 vaccine regimen (Ad26.Mos4.HIV complemented with a mix of a mosaic and clade C gp140) was evaluated in the phase 3 Mosaico trial (NCT03964415) in men who have sex with men and transgender individuals in the Americas and Europe. The study was discontinued in January, 2023, after an interim review showed that the vaccine regimen was not effective in preventing HIV-1 acquisition.[18] The final analysis of Mosaico is not yet available. Although disappointing, the findings from both the Mosaico and Imbokodo trials will help guide future research efforts in HIV-1 vaccine development, possibly by reducing reliance on this non-human primate model or promoting the use of well defined immunological markers supported by compelling evidence of a mechanistic correlate of protection.

The Imbokodo trial enrolled only women, which limits the generalisability of the results. In addition, Imbokodo was conducted in five countries, with most participants enrolled in South Africa; this setting could potentially limit the generalisability of the results to other parts of southern and eastern Africa given that HIV-1 incidence varies by region and high rates of exposure were observed in the Imbokodo trial (with the numerically highest exposure rate observed in South Africa). Furthermore, the predominant circulating clade in South Africa is clade C, which limits the generalisability of the findings beyond a predominantly subtype C HIV-1 epidemic. Nevertheless, Imbokodo was well executed despite challenges posed by the COVID-19 pandemic. The COVID-19 surge in participating countries started during the trial, and the fourth vaccination was administered during hard lockdowns. Retention rates were still high; 93% of participants completed all study vaccinations. No effect of COVID-19 on the assessment of the primary efficacy endpoint was observed.

In conclusion, Ad26.Mos4.HIV given with clade C gp140 did not provide protection against HIV-1 acquisition in southern African women aged 18–35 years at risk of acquiring HIV-1. Despite the availability of treatment for people living with HIV-1, acquisition rates remain persistently high, and more interventions and strategies are urgently needed to reduce the impact of HIV-1. The results from the Imbokodo trial are important scientific findings in the ongoing search for a vaccine to prevent HIV-1 acquisition; further ongoing immunological evaluations and correlative research could help to improve vaccine design.

Contributors

GEG and PBG directly accessed and verified the data reported in this Article. All authors had full access to the study data, critically reviewed the manuscript, and approved the final version. They all accept responsibility for submitting for publication. GEG contributed to the conceptualisation of this study, methodology, investigation, resources, data curation, writing of the original draft, data visualisation, and supervision. KM contributed to the investigation, resources, supervision, and project administration. LL contributed to the conceptualisation of this study, methodology, formal analysis, data visualisation, and supervision. SN contributed to the methodology and formal analysis. PBG contributed to the conceptualisation of this study, methodology, data validation, formal analysis, resources, data curation, writing of the original draft, data visualisation, supervision, project administration, and acquisition of funding. JH contributed to the conceptualisation of this study, methodology, software, data validation, resources, supervision, project administration, and acquisition of funding. OH contributed to the formal analysis, investigation, and data visualisation. MJ contributed to the conceptualisation of this study, methodology, and formal analysis. AL contributed to the conceptualisation of this study, methodology, and supervision. PM contributed to the conceptualisation of this study, methodology, and project administration. MJM contributed to the supervision, methodology, investigation, and acquisition of funding. JAO contributed to the methodology, supervision, and project administration. DJS contributed to the conceptualisation of this study and supervision. JvD contributed to the formal analysis and investigation. ANT contributed to the investigation and resources. WW contributed to the data validation and formal analysis. AT contributed to the project administration. GDT contributed to the conceptualisation of this study, methodology, investigation, resources, data curation, writing of the original draft, supervision, project administration, and acquisition of funding. JVH contributed to the conceptualisation of this study, methodology, and supervision. HS contributed to the conceptualisation of this study, methodology, and supervision. ES contributed to the conceptualisation of this study, methodology, and writing of the original draft. DHB contributed to the

conceptualisation of this study and methodology. JGK contributed to the conceptualisation of this study, methodology, resources, supervision, project administration, and acquisition of funding. LC contributed to the conceptualisation of this study, methodology, investigation, resources, data curation, writing of the original draft, data visualisation, and supervision. MGP contributed to the conceptualisation of this study, resources, supervision, project administration, and acquisition of funding. SB contributed to the supervision. FT contributed to the conceptualisation of this study, methodology, investigation, resources, data curation, writing of the original draft, data visualisation, and supervision.

Declaration of interests

GEG's institution (the South African Medical Research Council) has received funding from the US National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation. KM was a protocol co-chair for the Imbokodo trial. LL is a consultant for Janssen Infectious Diseases. SN, DJS, JvD, WW, JVH, HS, MGP, and FT were employees of Janssen Pharmaceuticals at the time of this study and are stockholders of Johnson & Johnson. AL's institution has received funding from the NIH; outside the submitted work, AL has received consulting fees from Harvard University, and his institution has received funding from Janssen Pharmaceuticals. PM is an employee and stockholder of CureVac. MJM's institution (Fred Hutchinson Cancer Center) has received funding, including for laboratory equipment purchases, from the HIV Vaccine Trials Network (HVTN) Laboratory Center (grant number 5UM1AI068618) and Seattle-Lausanne Clinical Trials Unit; outside the submitted work, her institution has received funding, including for laboratory equipment purchases, from the Scripps Consortium for HIV/AIDS Vaccine Development Subaward, National Institute of Allergy and Infectious Diseases (NIAID) Human Immunology Project Consortium 3, Bill & Melinda Gates Foundation Comprehensive Cellular Vaccine Immune Monitoring Consortium, and Bill & Melinda Gates Foundation Collaboration for AIDS Vaccine Discovery; her institution has received funding, including for laboratory equipment purchases, supporting SARS-CoV-2 vaccine laboratory studies from the COVID-19 Prevention Network (NIAID), Janssen Pharmaceuticals, Infectious Diseases Clinical Research Consortium (NIAID), Sanofi Pasteur, Moderna, and Regeneron; her institution has received funding, including for laboratory equipment purchases, supporting HIV and other vaccine trials and laboratory studies from International AIDS Vaccine Initiative, Janssen Pharmaceuticals, and Vir Biotechnology; and she has participated in scientific advisory boards for the Ragon Institute and Keystone Symposia, and on a board of scientific counsellors for the NIH Vaccine Research Center. GDT's institution (Duke University) has received NIH funding through the HVTN (grant numbers 5UM1AI068614 and 5UM1AI068618); GDT has served as a consultant for and received funding to her institution through Janssen Pharmaceuticals; is a reviewer for the Gilead Research Scholar Program; and has served on the board of scientific counsellors for the NIH Vaccine Research Center. DHB is a co-inventor on HIV vaccine patents that have been licensed to Janssen Pharmaceuticals. SB has received grant funding from Gilead Sciences, Merck, GSK, and ViiV. All other authors declare no competing interests.

Data sharing

The complete de-identified participant dataset and related documents, including the study protocol and statistical analysis plan, will be made available to the public via the ATLAS Science Portal at the time of publication of this Article.

For more on the **data available via the ATLAS Science Portal** see https://atlas.scharp.org/cpas/project/HVTN%20Public%20Data/begin.view

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