ChAdOx1 nCoV-19 (AZD1222) Vaccine in People Living With and Without HIV

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Abstract

Coronavirus disease 2019 (COVID-19) is a public health emergency of international concern[1]. People living with HIV (PLWH) are at increased risk for adverse COVID-19 outcomes compared with HIV-negative individuals[2-5], and are a high-risk group for COVID-19 prevention[4]. The ChAdOx1 nCoV-19 (AZD1222) vaccine has demonstrated safety and efficacy against COVID-19 in clinical trials[6-8]. To date, there are no reports on the safety and immunogenicity of this, or any COVID-19 vaccine, in PLWH, and reports on the immunogenicity of COVID-19 vaccines in Africa are limited[9]. Here, we show comparable safety and immunogenicity of two doses of ChAdOx1 nCoV-19 between PLWH and HIV-negative individuals in South Africa. Furthermore, in PLWH previously exposed to SARS-CoV-2, antibody responses increased substantially from baseline following a priming dose, with modest increases after a booster dose. Full-length spike and receptor-binding domain IgG geometric mean concentrations after a single dose of ChAdOx1 nCoV-19 in PLWH previously exposed to SARS-CoV-2 were 6.49–6.84-fold higher than after two doses in those who were SARS-CoV-2 naïve at enrollment. Neutralizing antibody responses were consistent with the antibody-binding responses. This is the first report of a COVID-19 vaccine specific to PLWH, and specific to Africa, and demonstrates favorable safety and immunogenicity of ChAdOx1 nCoV-19 in PLWH.

Background

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are being deployed globally following evidence of their safety and efficacy against coronavirus disease 2019 (COVID-19)[7,10-14]. Included among the first-generation COVID-19 vaccines authorized for emergency use is ChAdOx1 nCoV-19 (AZD1222), a nonreplicating simian adenovirus vector vaccine, which expresses the full-length spike (FLS) of the SARS-CoV-2 spike glycoprotein gene[8,15]. Immunogenicity studies have shown that ChAdOx1 nCoV-19 induces antibody responses specific to the spike protein, as well as to the receptor-binding domain (RBD) of the cleaved spike protein 28 days after a single dose in all age groups, including in adults aged ≥70 years, with a clear booster dose effect also apparent in all age groups[16]. Assessing the safety and efficacy of COVID-19 vaccines in different populations is essential. To date, there have been no published reports on the safety and immunogenicity of ChAdOx1 nCoV-19, or other COVID-19 vaccines in people living with HIV (PLWH). Furthermore, there are limited published reports from Africa on the immunogenicity of any COVID-19 vaccine[9].

PLWH are at greater risk for infectious diseases such as influenza, including while being treated with antiretroviral treatment (ART)[17-19], and are at higher risk for severe COVID-19 disease following SARS-CoV-2 exposure compared with HIV-negative individuals[3,20-24].

The Centers for Disease Control and Prevention (CDC) advises that PLWH can choose to be vaccinated against COVID-19, but may have reduced immune responses to the vaccine[25], while the World Health Organization recommends that PLWH are to be immunized with COVID-19 vaccines[26,27]. Although there are an estimated 38 million PLWH globally, there is limited knowledge on the safety and immunogenicity of COVID-19 vaccines in PLWH. This is particularly pertinent to sub-Saharan Africa where 67.6% of the world's PLWH, including 7.5 million in South Africa[28-30].

We report here interim results from a multi-center, randomized, double-blind, placebo-controlled phase 1b/2 trial assessing the safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine in people living with and without HIV in South Africa.

Trial design and analysis set

Overall, 104 PLWH (August 17, 2020 to November 12, 2020) and 70 HIV-negative individuals (June 24, 2020 to July 29, 2020) were enrolled in the intensive safety and immunogenicity cohort. One PLWH and 12 HIV-negative participants were excluded from all analyses due to a positive PCR tests for SARS CoV-2 at the time of randomization. A further one PLWH and two HIV-negative participants were excluded from all immunogenicity analyses due to absence of baseline serology. Thirty-two of 102 PLWH (31.4%) and 3 of 56 HIV-negative participants (5.4%) tested seropositive (RBD IgG positive) for SARS-CoV-2 at the time of randomization. The difference in these proportions is likely due to different enrollment dates of PLWH and HIV-negative participants: the former were enrolled after the first wave of COVID-19 and were therefore more likely to have been exposed to SARS-CoV-2 compared with HIV-negative participants who were enrolled at an earlier date. After excluding participants for positive SARS CoV-2 PCR tests or unavailable serology results at baseline, 56 HIV-negative participants (28 ChAdOx1 nCoV19; 28 placebo) received the trial intervention priming dose, in addition to 102 PLWH (52 ChAdOx1 nCoV19; 50 placebo).

At various points in the trial between priming dose and before day 42 (14 days post booster dose), an additional 5 PLWH and 9 HIV-negative participants were excluded from further analyses because of a positive SARS-CoV-2 PCR test (**Figure 1**). Furthermore, 1 HIV-negative participant in the placebo group was withdrawn from the trial (between receiving the priming and booster doses) due to previously undisclosed history of mental illness, and 3 PLWH (1 placebo, 2 ChAdOx1 nCoV19) missed their day 42 study visit (**Figure 1**).

Participant demographic characteristics

Demographic characteristics of the overall population excluding participants who had a positive SARS CoV-2 PCR test but including participants with no baseline serology (**Figure 1**), show that 62.1% of HIV-negative participants were male, compared with 26.2% of PLWH. The majority of participants (99.4%) were Black (**Table 1**). The median age of HIV-negative participants was lower than that of PLWH (32 vs 40 years, respectively). HIV-negative participants had a lower prevalence of underlying hypertension (1.7% vs 10.7%) and chronic respiratory conditions (0% vs 15.5%) compared with PLWH, respectively. The proportion of individuals with a body mass index 30 to 39.9 kg/m^2 was similar between HIV-negative participants and PLWH (20.7% vs 22.3%). PLWH were stable on ART with a median CD4+ cell count of 695 cells/μL, a CD4+ percentage of 36%, and a median viral load of 10 copies/mL (**Table 1**). Most PLWH had received ART for between 1 and 5 years or over 5 years.

The demographic characteristics of participants who were seronegative for SARS-CoV-2 at the time of randomization and therefore eligible for inclusion in post-booster-dose immune response analyses, as well as the demographic characteristics of participants who were seropositive for SARS-CoV-2 at the time of

randomization, were similar to those of the overall population (**Extended Data Tables 1** and **2**).

Safety and reactogenicity data

Safety and reactogenicity analyses included all randomized individuals who received ≥1 dose of trial intervention (56 HIV-negative participants and 102 PLWH) from enrollment until January 15, 2021. Local reactogenicity was assessed for 7 days after both priming and booster vaccine doses. In HIV-negative participants and PLWH, tenderness, hardness, bruising, and itching at the injection site were the most commonly reported local reactions in vaccine and placebo recipients alike (**Figure 2**). These events were less common among HIV-negative participants than PLWH, and in both groups, were predominantly mild or moderate in intensity, with moderate symptoms reported more often in the first 2 days after vaccination. Among both HIV-negative participants and PLWH, there were no increases in reported local reactions after receiving the booster dose. Headache, joint and muscle pain, and weakness were the most commonly reported systemic reactions, occurring in almost one-quarter of participants in the first 2 days after the priming dose (**Figure 2**). Symptoms were mild or moderate in intensity over the first 48 hours in HIV-negative participants and PLWH. Fever, rigors, and sweating, lasting up to 7 days, were less commonly reported in HIV-negative participants than in PLWH. Detailed adverse event (AE) data are presented in **Extended Data Tables 3** and **4**. Overall, 7 serious AEs (SAEs) occurred (**Extended Data Table 5**). Six of these occurred in HIV-negative participants (4 in those receiving the vaccine, 2 in those receiving placebo) of which 5 were deemed unrelated to the trial intervention. One HIV-negative participant reported a temperature of 40.5°C following the primary dose. However, the temperature resolved within 1 day with paracetamol, and no reactions to the booster dose were reported. In PLWH, there was 1 SAE in a participant who received placebo treatment. This was deemed unlikely related to the trial intervention.

There were few hematology abnormalities and no clinically important worsening was observed in hematology or chemistry panels in any of the trial groups (**Extended Data Figures 1** and **2**). PLWH had mild levels of alkaline phosphatase elevation in both vaccine and placebo groups through the trial. There were four potassium level increases graded as severe or higher due to samples being hemolyzed and all subsequent blood draws showed normal levels of potassium.

Of the 32 participants with a positive SARS-CoV-2 PCR test during the trial, only 1 (PLWH) displayed moderate COVID symptoms, which occurred between day 28 (28 days post priming dose) and day 42 (14 days post booster dose) (**Extended Data Table 6**). The remaining participants with a positive SARS-CoV-2 PCR test were asymptomatic (6 HIV-negative participants, 1 PLWH), had mild symptoms (8 HIV-negative participants, 5 PLWH), or had other symptoms that did not meet the protocol definition of mild COVID-19 disease (10 HIV-negative participants, 1 PLWH).

Vaccine-induced antibody responses

Concentrations of FLS immunoglobulin G (IgG), RBD-binding IgG, and SARS-CoV-2 neutralizing titers were assessed at baseline (day 0), day 28, and day 42. Immunized participants showed a strong, vaccine-induced serum IgG response against FLS and RBD, regardless of HIV status, which increased with the booster dose (**Figure 3a**). Twenty-eight days after the priming dose, the median FLS IgG geometric mean concentration (GMC) was163.7 binding antibody units (BAU)/mL (95% confidence interval [CI], 89.9–298.1; n=36) for PLWH and 112.3 BAU/mL (95% CI, 61.7–204.4; n=23) for HIV-negative participants. A booster response was measured at day 42, with a median GMC of 453.1 BAU/mL (95% CI, 267.4–767.7; n=32) in PLWH, and 504.9 BAU/mL (95% CI, 337.1–756.2; n=23) in HIV-negative participants (**Extended Data Table 7**). Similar IgG response patterns were observed for ChAdOx1 nCoV-19-induced geometric mean RBD-binding IgG concentrations (**Extended Data Table 8**). Seropositivity for either FLS or RBD IgG was similar between the PLWH and HIV-negative populations who received the vaccine. At day 28, seropositivity for FLS IgG was 86.1% (95% CI, 71.3–93.9; n=36) in PLWH and 78.3% (95% CI, 58.1–90.3; n=23) in HIV-negative participants (**Extended Data Table 7**).

Immunogenicity was also evaluated in PLWH based on SARS-CoV-2 serostatus at baseline, excluding patients with a positive SARS-CoV-2 PCR test, enabling a *post hoc* analysis of immune responses in this group following vaccination (**Figure 3b**). The same analysis was not possible for the HIV-negative group because only 3 participants were seropositive for SARS-CoV-2. At day 28, both FLS and RBD IgG concentrations increased substantially from baseline after a single dose, with modest increases observed by day 42 (**Extended Data Tables 9** and **10**). The IgG GMCs following a single priming dose of ChAdOx1-nCoV-19 in PLWH who were SARS-CoV-2 seropositive at enrollment were 6.49–6.84-fold higher than the IgG GMCs following a booster dose in PLWH who were SARS-CoV-2 naïve at baseline (**Extended Data Tables 9** and **10**).

Pseudotyped virus neutralization assays

Neutralization activity was assessed for 26 HIV-negative participants vaccinated with ChAdOx1 nCoV-19. The geometric mean titers (GMT) of SARS-CoV-2 neutralizing antibodies in this group strongly correlated with antigen-specific IgG GMCs on days 28 and 42. At day 0, GMT of 2 of the 25 HIV-negative participants was inhibitory dilution (50%) (ID50) 31, increasing to a GMT of 135 at day 28, among 13 of the 22 participants. Neither of the two participants who showed neutralization activity at day 0 subsequently showed a >2-fold increase at day 28. At day 42, GMT neutralization activity in the 20 assessed participants was ID50 316. Of the 13 participants who had neutralization activity at day 28, results from 12 participants were available at day 42. Of these 12 participants, only 6 showed a ≥2-fold increase in neutralization activity at day 42 (**Extended Data Table 11**). Neutralizing antibody activity was also assessed in all PLWH samples that were RBD seropositive at day 42 using a mouse leukemia virus backbone neutralization assay. Of these, data were obtained for n=34 (64%) of the samples. In the remaining 18 samples, non-specific neutralization activity likely due to ART precluded the determination of titers, and these were not further analyzed. Of the 18 PLWH who were RBD seronegative at baseline, 17 mounted neutralizing responses, with GMT neutralization activity (ID50 [95% CI] 151.5 [54.8–419.0]) n=17) that was similar to that of 18 HIV-negative participants who were RBD seronegative at baseline (ID50 [95% CI] 394.2 [242.0–642.1]) (**Figure 4**).

Discussion

This interim phase 1b/2a analysis reports for the first time the safety and immunogenicity of a COVID-19 vaccine in PLWH. Our results show that two doses of ChAdOx1 nCoV-19 were safe and well tolerated in PLWH, with similar FLS- and RBD-binding IgG and SARS-CoV-2 neutralizing response patterns in PLWH and HIV-negative SARS-CoV-2–naïve participants following priming and booster doses of the vaccine. The findings aligned with previously reported immunogenicity for this vaccine across all adult age groups[16]

Antibody responses to FLS and RBD viral proteins induced by each dose were also seen in PLWH who had previously been exposed to SARS-CoV-2. Notably, previous infection with SARS-CoV-2 in PLWH was associated with robust immune responses after a single dose of ChAdOx1-nCoV19, with GMCs exceeding by 6.49–6.84-fold those seen post booster dose in vaccine recipients who were seronegative at enrollment, as similarly recently reported in HIV-negative participants[31].

In our trial, development of neutralizing titers after priming and booster doses of ChAdOx1 nCoV-19 correlated with antibody responses to FLS and RBD viral antigens in HIV-negative participants and in PLWH. Taken together, these findings suggest that vaccination with ChAdOx1 nCoV-19 may consolidate the immune response and drive long-term immune memory, providing a protective benefit to this population, regardless of prior SARS-CoV-2 exposure. Neutralizing antibodies have been implicated as correlates of protection from COVID-19 in preclinical challenge studies[32,33] and, in a previous clinical trial, neutralizing antibodies developed in >99% of participants after vaccination with ChAdOx1 nCov-19, with higher levels in boosted compared with non-boosted groups.[16] However, to date no correlates of protection have been defined from clinical COVID-19 vaccine studies.

The majority of AEs reported in PLWH and HIV-negative participants were mild or moderate in intensity, which supports the previously reported safety profile of ChAdOx1 nCoV-19[7-9]. Reactogenicity, assessed 7 days after the priming and booster doses of vaccine, was lower in HIV-negative participants than in PLWH, with symptoms predominantly mild or moderate in intensity. In both populations, fewer AEs were reported after the booster dose than after the priming dose and no clinically important worsening was observed in hematology or chemistry panels compared with placebo.

Assessing the safety and immunogenicity of COVID-19 vaccines in different populations is essential, particularly in those who are at increased risk for severe disease and death from COVID-19 because of, for example, immunodeficiency, comorbidities, and/or societal inequities, such as poverty or reduced access to care[34].

In the United States of America, PLWH have been shown to have a greater risk for COVID-19 hospitalization compared with HIV-negative individuals[20], while studies in the United Kingdom have shown that underlying HIV infection is associated with a greater risk for COVID-19 death, with higher associations in people of Black ethnicity compared with non-Black individuals[5]. In South Africa, HIV infection has been associated with an increased risk of death from COVID-19, irrespective of HIV-1 viral load and immunosuppression[35].

Conducting vaccine trials in Africa is vital to ensure that approved vaccines for COVID-19 will be safe and effective in this geography, particularly given the burden of HIV in sub-Saharan Africa[30]. The SARS-CoV-2 spike genome has recently accumulated mutations, resulting in the emergence of variants, including the B.1.351 (N501Y.V2) lineage first identified in South Africa[36]. In the overall analysis of the present phase 1b/2 trial, published elsewhere,[9] the two-dose regimen of ChAdOx1 nCoV-19 did not show protection against non-hospitalized mild to moderate COVID-19 in young HIV-negative adults in South Africa. This lack of efficacy was suggested to be due to the dominance of the B.1.351 variant. In those participants, the ChAdOx1 nCoV-19 vaccine induced strong neutralizing antibodies 28 days after the first dose, which increased following a booster dose given between 21 and 35 days later, yet neutralizing activity was reduced or undetected against the B.1.351 variant[9].

Limitations of our clinical trial include the small sample size of HIV-negative participants who were seropositive for SARS-CoV-2, precluding comparisons between SARS-CoV-2 seropositive PLWH and SARS-CoV-2 seropositive HIV-negative participants. Another constraint is that cell-mediated immune responses in the participants were not investigated. Previous studies have shown that spike-specific T-cell responses are induced by ChAdOx1 nCoV-19 in vaccine recipients as early as 7 days after the priming dose[16]. Furthermore, others have shown that some cases of asymptomatic SARS-CoV-2 exposure are associated with a cellular immune response without seroconversion, suggesting a role for disease-controlling specific T cells in the absence of a neutralizing antibody response[37]. Another limitation is that PLWH included in this trial were receiving ART for ≥3 months and had an HIV-1 viral load <1000 copies/mL, which may not be representative of the PLWH population with CD4+ counts <500 cells/μL who may be at highest risk for severe COVID-19 disease and poor outcomes. Furthermore, ART can interfere with the performance of neutralization assays, which explains the relatively low number of PLWH whose sera provided neutralizing antibody data in this trial.

Given the prevalence of emerging SARS-CoV-2 variants of concern, further trials in PLWH and in South Africa, which include analyses of cellular immune responses, are warranted, as are additional trials to correlate vaccine-induced immunogenicity with protection from COVID-19 in this population. However, the findings from this first report of administration of a COVID-19 vaccine specific to PLWH, and specific to Africa, demonstrate favorable safety and immunogenicity of ChAdOx1 nCoV-19 in PLWH. Furthermore, we also report that previous SARS-CoV-2 exposure in PLWH may not compromise the vaccine's protective benefit

Methods

Clinical trial design and trial participants

This is an interim analysis of the continuing, adaptive, phase 1b/2, double-blind, randomized, placebo-controlled COV005 trial, assessing the safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine in South Africa, details of which have previously been published[9]. Briefly, the trial began enrolling on June 24, 2020, and is being carried out in 7 South African locations in accordance with principles of the Declaration of Helsinki and Good Clinical

Practice Guidelines[7]. Full details of the approved trial protocol (version 6.0) are available[38]. All participants were fully informed about trial procedures and possible risks prior to giving written, informed consent.

This sub-analysis of the COV005 trial assessed the safety and immunogenicity of ChAdOx1 nCoV-19 in healthy adults aged 18–65 years living with and without HIV in South Africa. HIV-negative status was tested prior to enrollment. People living with HIV-1 (PLWH) had been in receipt of antiretroviral treatment for ≥3 months and had an HIV-1 viral load <1000 copies/mL within 2 weeks of randomization. All participants were required to test seronegative for hepatitis B surface antigen. Participants were excluded if they had Grade ≥2 abnormalities in full blood count, urea and electrolytes tests, or liver function tests, according to the Division of AIDS Grading Criteria (version 2.1, July 2017). Full exclusion and inclusion criteria are provided in the trial protocol[38].

PLWH and HIV-negative participants were randomized 1:1 to receive two intramuscular injections of ChAdOx1 nCoV-19 or saline placebo (0.9% sodium chloride), separated by an interval of 28 days. Details of the randomization procedure have been previously published[7]. As described in Madhi et al.[9], between June 24, 2020 and July 29, 2020, a cohort of 70 HIV-negative individuals were enrolled first (Group 1) for intensive safety and immunogenicity monitoring, followed by wider enrollment of HIV-negative individuals (Group 2) for further safety, immunogenicity, and efficacy assessment (data not included in this report). Between August 17, 2020 and November 12, 2020, PLWH (Group 3) were enrolled for intensive safety and immunogenicity assessment. The present analysis utilizes and compares data obtained from Group 1 (HIV-negative) and Group 3 (PLWH), which both involved intensive immunogenicity monitoring.

The original protocol (version 1.0) included a nasal swab to test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at the time of randomization, irrespective of symptomatology, as well as blood samples taken for COVID-19 serology analysis. Following enrollment of the initial 24 participants in Group 1, 7 (29%) participants had a positive polymerase chain reaction (PCR) test for SARS-CoV-2 on nasal swabs done on the day of randomization. The protocol was therefore amended to include screening for SARS-CoV-2 via PCR within 96 hours of randomization and a positive SARS-CoV-2 PCR test being added as an exclusion criterion, implemented prior to starting enrollment of PLWH.

For Group 1 (HIV-negative participants), the sample size was increased from 50 to 70 to replace individuals who tested positive for SARS-CoV-2 infection at time of randomization during the initial phase of enrollment. For Group 3 (PLWH), the sample size was increased from 50 to 100 owing to a high (35%–45%) force of SARS-CoV-2 infection having been opportunistically identified in residual blood samples from PLWH in South Africa as the first wave was subsiding[39]. We estimated that the increase in sample size would result in approximately 50 individuals in Group 1 and 70 in Group 3 who would remain seronegative for COVID-19 throughout the trial and therefore evaluable for the main immunogenicity analysis that was to be limited to those who were SARS-CoV-2 naïve at enrollment.

The primary endpoint in both HIV-negative participants and PLWH was the safety, tolerability, and reactogenicity profile of ChAdOx1 nCoV-19, as assessed by local and systemic reactogenicity and adverse events (AEs). In PLWH, the co-primary endpoint was cellular and humoral immunogenicity of ChAdOx1 nCoV-19, as assessed by quantification of serum antibody (IgG) to SARS-CoV-2 full-length spike (FLS) protein, receptor-binding domain (RBD), and virus neutralizing antibody (NAb) assays against live and/or pseudotyped SARS-CoV-2 virus. In HIV-negative participants, the co-primary endpoint was the efficacy of ChAdOx1 nCoV-19 against mild to severe COVID-19, as assessed by the number of PCR-positive COVID-19 disease cases occurring in participants who were COVID-19 naïve at the time of randomization and is reported elsewhere[9].

Co-primary endpoints were assessed for 7 days after receipt of vaccine, and unsolicited AEs for 28 days following vaccination. Additional post hoc analyses examined immunogenicity in PLWH who were seropositive for SARS-CoV-2 exposure prior to their first dose of vaccine.

Baseline assessments included review of inclusion and exclusion criteria, medical history, vital signs measurement, history-directed clinical examination, and collection of serum for SARS-CoV-2 serology. All participants underwent PCR testing for SARS-CoV-2 within 96 hours of randomization, and on days 7, 14, 28, 35, 42, and 56 post-randomization. Baseline SARS-CoV-2 serostatus was determined by testing participant serum with a colorimetric, plate-based receptor-binding domain (RBD) IgG ELISA assay performed as previously described at the National Institute for Communicable Diseases (South Africa)[40]. In addition, participants were regularly reminded to contact the trial site if they experienced specific symptoms associated with coronavirus disease 2019 (COVID-19). The consort diagram is shown in **Figure 1**.

Vaccine manufacturing

ChAdOx1 nCoV-19 is formulated at a dose of 5×10^{10} virus particles. In this trial, three different batches of ChAdOx1 nCoV-19 were used. The first two batches (batch K.0008 and batch K.0011) were manufactured and vialed by Advent (Pomezia, Italy), and the third (batch A03367) was produced by COBRA Biologics (Keele, United Kingdom) and vialed by Symbiosis (Sterling, UK). According to analytical analysis, vaccines from all lots were not expected to have clinically significant differences in reactogenicity, immunogenicity, or efficacy. All vaccine batches were manufactured according to Good Manufacturing Practice and approved by the Medicines and Healthcare Products regulatory agency in the United Kingdom. Of the participants included in the safety analysis, 34, 32, and 15 received batches K.0008, K.0011, and A03367 for their priming dose, respectively. For the booster dose, 28 received batch K.0008, 25 received batch K.0011, and 28 received batch A03367.

Safety/adverse events

In this interim analysis, we report on solicited and unsolicited AEs within 7 days of the first dose of vaccine or placebo, and within 7 days of the booster dose. Safety evaluations included analysis of full blood count, urine and electrolytes, and liver function tests, which were all assessed prior to randomization, on days 3 and 7 post-randomization, on the day that the booster dose was administered, and on days 14 and 28 after the booster dose. Follow-up will continue for 12 months after enrollment. This analysis includes adverse event data reported through January 15, 2021.

PCR testing

PCR testing for SARS-CoV-2 infection at baseline and throughout the trial was performed as previously described[41,42] using Emergency Use Authorization assays developed by the Centers for Diseases Control and Prevention (CDC). Briefly, nasopharyngeal swabs were taken from participants, processed to extract nucleic acid, and evaluated by real-time, reverse transcriptase-PCR assays specific to two target regions within the nucleocapsid gene of the SARS-CoV-2 viral genome. An additional assay, specific to the human ribonuclease P gene, was run as a sample extraction and processing control. All PCR testing was performed in one of two trial-site laboratories, Vaccines and Infectious Diseases Analytics Research Unit (VIDA, Johannesburg) or University of Cape Town Lung Institute (Cape Town, South Africa)[9].

Immunogenicity testing

Immunogenicity analyses were performed on day 0, before administration of the first placebo or vaccine (priming dose), on day 28 post prime, the day that the second dose of placebo or vaccine (booster dose) was administered, and on day 42, 14 days post booster. Singleplex bead-based immunoassays were developed on the Luminex platform to quantitatively measure serum IgG to FLS and RBD. The expression plasmids encoding SARS-CoV-2 FLS and RBD were obtained from Florian Krammer (Mount Sinai, New York United States). The recombinant FLS and RBD proteins were expressed as described previously[40] and were coupled to magnetic microspheres (Bio-Rad, Philadelphia, PA United States) using a two-step carbodiimide reaction[43]. An in-house reference serum was developed by pooling convalescent serum from adult COVID-19 cases. This interim reference serum was calibrated against research reagent NIBSC 20/130. The NIBSC 20/130 research reagent for SARS-CoV-2 RNA (was obtained from the National Institute for Biological Standards and Controls and used for the development and evaluation of serological assays for the detection of antibodies against SARS CoV-2. (For details of the binding antibody units [BAU] for viral components see https://www.nibsc.org/). The BAU assigned to the in-house reference serum were 1,242 and 2,819/mL BAU/mL for RBD and FLS IgG, respectively. Serum samples collected prior to 2020 (n=31) were used for determination of assay specificity. Cut-offs of 32 BAU/mL and 26 BAU/mL for FLS and RBS IgG, respectively, were selected as thresholds indicative of SARS-CoV-2 infection, based on the highest values measured in pre-COVID-19 samples.

Clinical sensitivity of the assay in detecting past or current infection was assessed using serum samples obtained from randomly selected (n=15) participants who tested positive for SARS-CoV-2 by PCR and who had serial sampling before and after symptom onset, including cases with mild to moderate illness and asymptomatic infections. The clinical sensitivity of the IgG assay for both FLS and RBD was 75% for samples taken at 7 to 14 days following a positive SARS-CoV-2 PCR result, and 100% for samples taken after 14 days. The optimal serum/plasma and secondary antibody dilutions for the assay were 1:100 and 1:200, respectively. Samples exceeding the dynamic range of the assay were re-tested at higher dilutions (1:200–1:1000). Samples were analyzed in true duplicate and each plate included two in-house control sera. Bead fluorescence was read with the Bio-Plex 200 instrument (Bio-Rad) using Bio-Plex manager 5.0 software (Bio-Rad).

Two pseudovirus neutralization assays were used to determine serum concentrations of SARS-CoV-2 neutralizing antibodies. Samples from HIV-negative participants were tested using a SARS-CoV-2 Wuhan-1 D614G neutralization assay performed at the National Institute for Communicable Diseases (South Africa) as previously described[40]. For samples from PLWH, which may be impacted by antiretroviral therapies (ARVs), samples were first screened for ARV-mediated background activity using MLV envelope pseudotyped viruses in a mouse leukemia virus (MLV) backbone[44]. Those samples showing background presumed to be mediated by ARVs (34%) were excluded from further testing, while acceptable samples were then tested using a SARS-CoV-2-specific microneutralization assay in the same MLV backbone expressing Wuhan-1 D614G. We show high levels of concordance between D614G-mediated neutralization in these two assays using 56 samples tested head-to-head in both assays (**Extended Data Figure 3**).

Statistical analysis

Statistical analyses were performed using R, version 4.02[45]. For the primary safety objective, the sample size was 25 participants per trial arm in HIV-negative people and PLWH. For a serious event with a 0.01 rate of occurrence, the probability that 0 participants will experience this event is 0.778 in each group. For the primary immunogenicity endpoint, a sample size of 25 per group would have 80% power to detect a 48.4% difference in response rates between two groups, if the true response rate in the unvaccinated group was 10%. Additional power calculations for this trial have been previously published[38].

Declarations

Data availability

The authors declare that the data supporting the findings of this study are available within the paper and its supplementary information files.

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Author contributions

SAM conceived the trial, SAM is the national principal investigator. SAM, AI, CLC, GK, VB and AJP contributed to the protocol and design of the trial. SAM, AI, CLC, GK, VB, ALK and CT were responsible for the design and conduct of the trial, database design and development, site selection and training, data collection, data cleaning and interpretation of results. AI conducted the statistical analysis. SLB, QEB, CB, KD, LF, ALK and SDP are study site principal investigators and enrolled participants, collected data and contributed to manuscript preparation. SB, EH, AJ, MaM, MdM, FP, CT, AT and SvE contributed to the implementation of the trial at sites and/or data collection. PK, TH, CKM, TH, PK, LM, and TMG contributed to data generation and analysis. AM, contributed to sample processing, data generation and analysis. SAM, AI, CLC, VB, GK, JV, and PLM contributed to the preparation of the report.

Competing interests

Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19 (AZD1222). AstraZeneca reviewed the data from the trial and the final manuscript before submission, but the authors retained editorial control. SCG is cofounder of Vaccitech (a collaborator in the early development of this vaccine candidate) and named as an inventor on a patent covering use of ChAdOx1-vectored vaccines (PCT/GB2012/000467) and a patent application covering this SARS-CoV-2 vaccine (GB2003670.3, 13.03.2020). TL is named as an inventor on a patent application covering this SARS-CoV-2 vaccine and was consultant to Vaccitech. TLV and JV are employees of AstraZeneca.

Additional information

Supplementary information is available for this paper. Correspondence and requests for materials should be addressed to Shabir A. Madhi. Peer review information: *Nature* thanks the anonymous reviewers for their contribution to the peer review of this work. Reprints and permissions information is available at http://www.nature.com/reprints.

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Table

Table 1. Baseline demographics of the overall trial population, stratified by HIV status.

Characteristic	Overall	HIV-negative participants			PLWH		
	(N=161)	Overall (n=58)	Placebo (n=29)	Vaccine (n=29)	Overall (n=103)	Placebo (n=51)	Vaccine (n=52)
Median (IQR) age, years	37 (31–44)	32 (25–42)	31 (26–42)	34 (23–41)	40 (33–46)	41 (36–46)	37 (32–45)
Male, n (%)	63 (39.1)	36 (62.1)	19 (65.5)	17 (58.6)	27 (26.2)	11 (21.6)	16 (30.8)
Race, n (%)							
Black	160 (99.4)	58 (100)	29 (100)	29 (100)	102 (99)	51 (100)	51 (98.1)
White	1 (0.6)	0	0	0	1 (1)	0	1 (1.9)
BMI, kg/m^2, n (%)							
<18	12 (7.5)	7 (12.1)	4 (13.8)	3 (10.3)	5 (4.9)	1 (2)	4 (7.7)
18–24.9	68 (42.2)	26 (44.8)	15 (51.7)	11 (37.9)	42 (40.8)	18 (35.3)	24 (46.2)
25–29.9	46 (28.6)	13 (22.4)	4 (13.8)	9 (31)	33 (32)	16 (31.4)	17 (32.7)
30–39.9	35 (21.7)	12 (20.7)	6 (20.7)	6 (20.7)	23 (22.3)	16 (31.4)	7 (13.5)
Smoker, n (%)	61 (37.9)	27 (46.6)	12 (41.4)	15 (51.7)	34 (33)	16 (31.4)	18 (34.6)
Alcohol, n (%)	72 (44.7)	25 (43.1)	13 (44.8)	12 (41.4)	47 (45.6)	21 (41.2)	26 (50)
Health care worker, n (%)	3 (1.9)	1 (1.7)	1 (3.4)	0	2 (1.9)	1 (2)	1 (1.9)
Hypertension, n (%)	12 (7.5)	1 (1.7)	0	1 (3.4)	11 (10.7)	7 (13.7)	4 (7.7)
Respiratory system, n (%)	16 (9.9)	0	0	0	16 (15.5)	10 (19.6)	6 (11.5)
HbA1c, n (%)							
Low	12 (7.5)	2 (3.4)	0	2 (6.9)	10 (9.7)	5 (9.8)	5 (9.6)
Normal	145 (90.1)	53 (91.4)	26 (89.7)	27 (93.1)	92 (89.3)	46 (90.2)	46 (88.5)
High	4 (2.5)	3 (5.2)	3 (10.3)	0	1 (1)	0	1 (1.9)
ART, n (%)[†]							
NNRTI and 2 NRTIs	NA	NA	NA	NA	57 (76%)	29 (74.4%)	28 (77.8%)
INSTI and 2 NRTIs	NA	NA	NA	NA	11 (14.7%)	5 (12.8%)	6 (16.7%)
Boosted PI and 1 NRTI	NA	NA	NA	NA	4 (5.3%)	3 (7.7%)	1 (2.8%)
Boosted PI and 2 NRTIs	NA	NA	NA	NA	3 (4%)	2 (5.1%)	1 (2.8%)
Time on ART, n (%)							
<1 year	NA	NA	NA	NA	9 (12%)	4 (10.3%)	5 (13.9%)
1–<5 years	NA	NA	NA	NA	28 (37.3%)	12 (30.8%)	16 (44.4%)
≥5 years	NA	NA	NA	NA	38 (50.7%)	23 (59%)	15 (41.7%)
Median (IQR) CD4+ count, cells/μL	NA	NA	NA	NA	695 (512–929)	677 (500–889)	742 (540–953)
Median (IQR) CD4+ percentage	NA	NA	NA	NA	36 (30–41)	36 (29–41)	37 (32–41)
Median (IQR) detectable viral load, copies/mL	NA	NA	NA	NA	10 (10–50)	10 (10–28)	30 (10–105)
Median (IQR) time between doses, days	28 (27–28)	28 (28–28)	28 (28–28)	28 (28–28)	28 (25–28)	28 (26–28)	28 (23–28)
Median (IQR) time post-boost, days	14 (14–14)	14 (14–15)	14 (14–14)	14 (14–15)	14 (14–14)	14 (14–14)	14 (14–14)

Data exclude patients who were SARS-CoV-2 seropositive at baseline and include patients with no baseline serology available.

[†]Most (75%) were receiving an efavirenz-based regimen and 14.5% were receiving a dolutegravir-based regimen with 2 NRTIs, tenofovir and lamivudine or emtricitabine, and 1 participant received zidovidine and lamivudine. The remaining participants received a boosted PI-based regimen, either lopinavir/ritonavir or atazanavir/ritonavir, with either 1 or 2 NRTIs, including lamivudine, zidovudine, abacavir or tenofovir.

ART= antiretroviral treatment; BMI=body mass index; HbA1c=glycated hemoglobin measurement (indicator of diabetes); HIV=human immunodeficiency virus; INSTI=integrase strand transfer inhibitor; IQR=interquartile range; n=subpopulation number; NA=not applicable; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI= nucleoside and nucleotide reverse transcriptase inhibitors; PI, protease inhibitor; PLWH=people living with HIV; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Figures

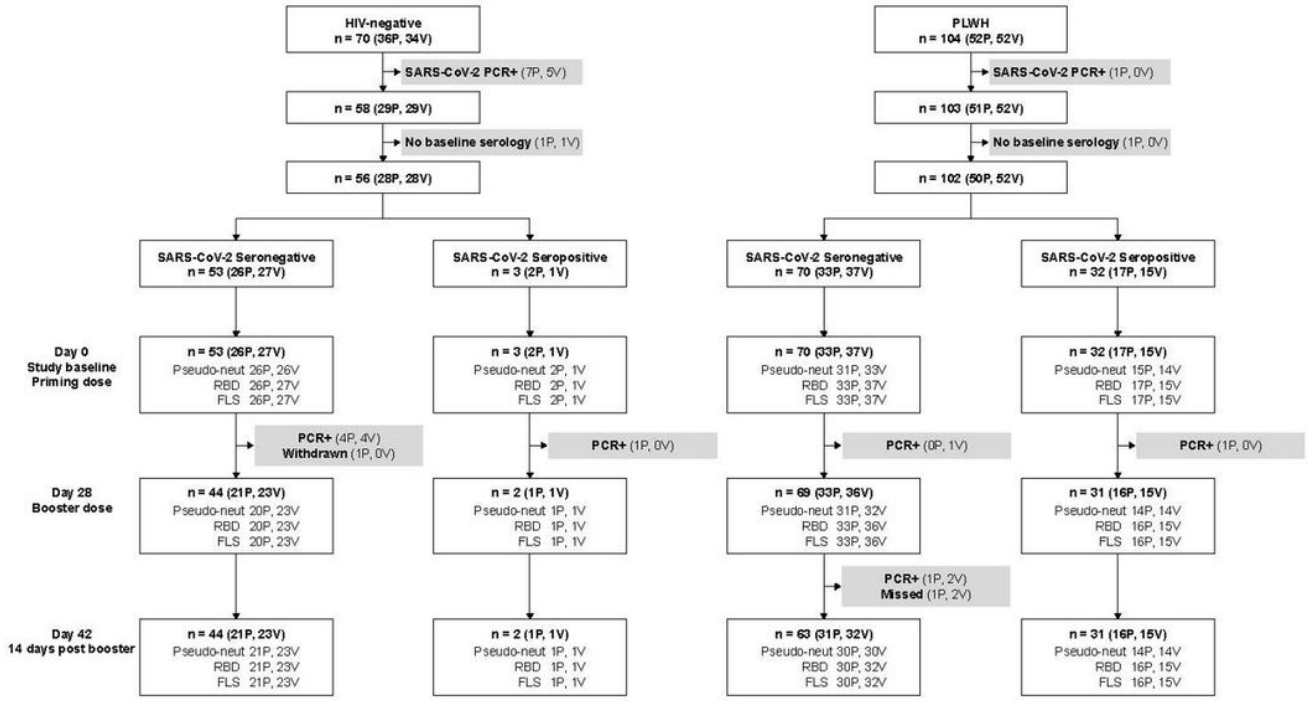

Figure 1

Consort diagram of participant follow-up and inclusion in immunogenicity analysis, stratified by SARS-CoV-2 serostatus (IgG positivity against RBD). Twenty-seven participants (21 HIV negative and 6 PLWH) were excluded from analysis because of a positive SARS-CoV-2 PCR test within the trial period. Three participants were excluded from the immunogenicity analysis owing to an absence of baseline serology. Twelve participants (1 withdrawn and 11 positive SARS-CoV-2 PCR tests) did not receive a booster dose. Three participants were excluded from analysis at day 42 as they were lost to follow-up. FLS=full length spike; HIV=human immunodeficiency virus; IgG=immunoglobulin G; n=number of participants; P=placebo; PCR=polymerase chain reaction; PLWH=people living with HIV; pseudo-neut=pseudoneutralization; RBD=receptor-binding domain; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; V=vaccine.

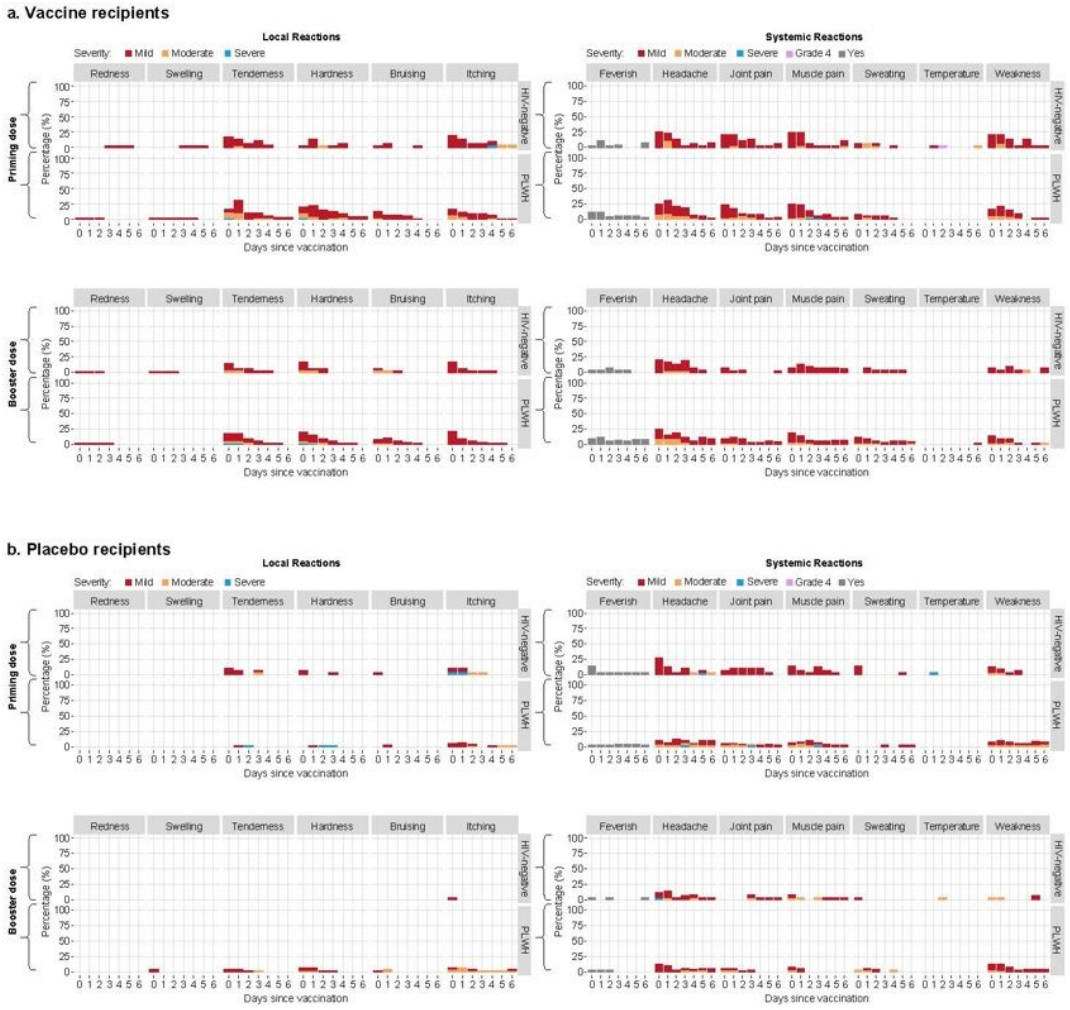

Figure 2

Solicited local and systemic adverse reactions in the 7 days after priming and booster doses stratified by a) vaccine recipients and b) placebo recipients. Day 0 is the day of the priming dose. The severity of adverse events was graded as mild, moderate or severe. HIV=human immunodeficiency virus; PLWH=people living with HIV.

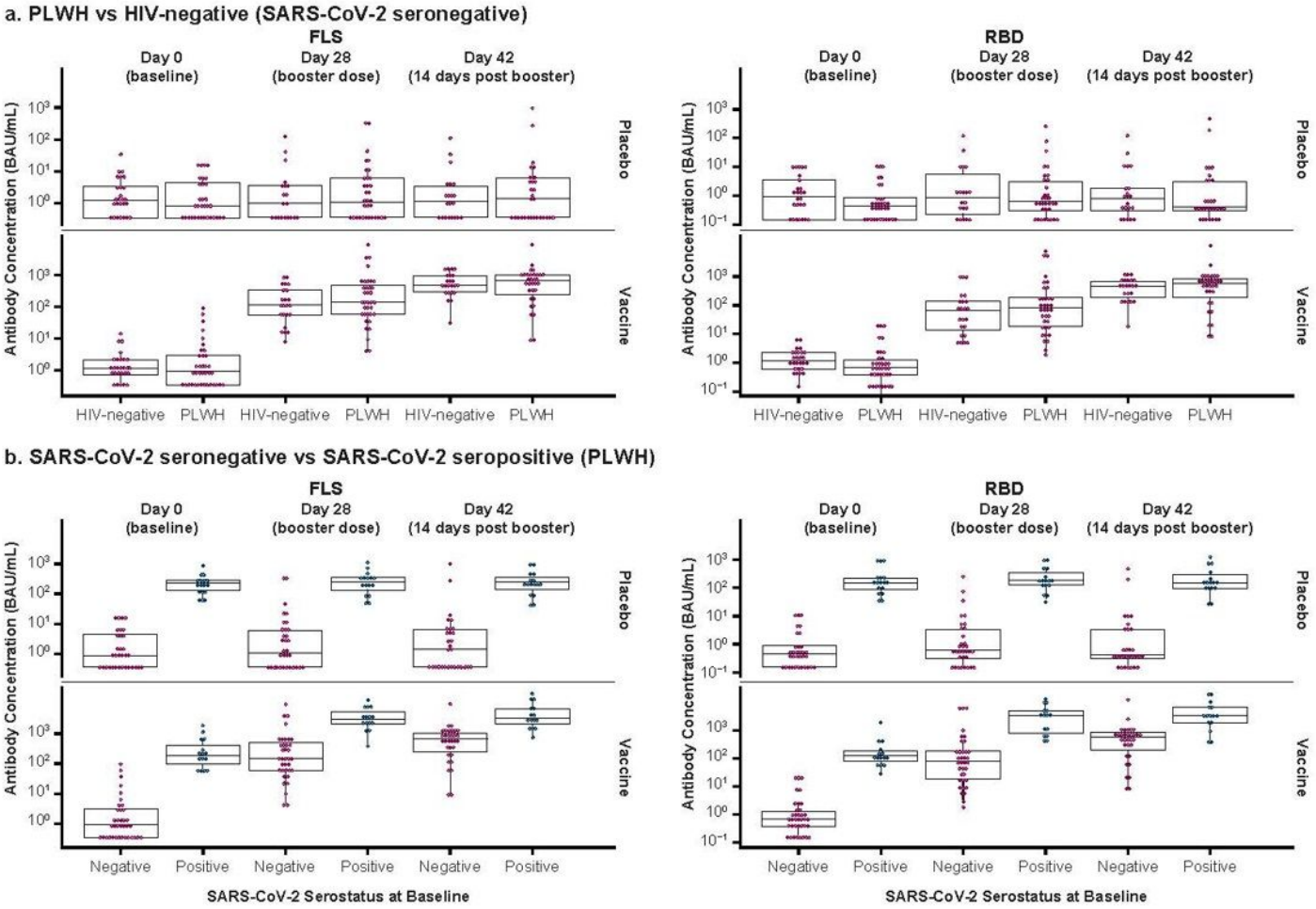

Figure 3

Immunogenicity to SARS-CoV-2 FLS and RBD protein stratified by a) HIV status and by b) SARS-CoV-2 serostatus at baseline in PLWH. Antibody responses to RBD and assessed at day 0 (baseline), day 28 (post-priming dose), and day 42 (14 days post-booster dose). Boxes denote interquartile ranges, and horizontal bars denote median antibody concentration in BAU/mL. BAU=binding antibody unit; FLS=full-length spike protein; HIV=human immunodeficiency virus; PLWH=people living with HIV; RBD=receptor-binding domain; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

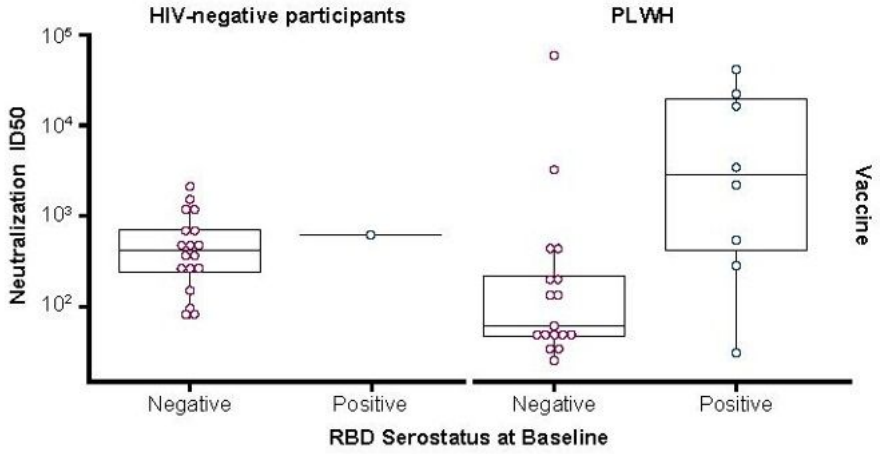

Figure 4

Pseudovirus neutralization responses on day 42 (14 days post booster). Samples below the limit of detection are not shown. Boxes denote interquartile ranges, and horizontal bars denote neutralization ID50. HIV=human immunodeficiency virus; ID50=inhibitory dilution (50%); PLWH=people living with HIV; RBD=receptor-binding domain.

Supplementary Files

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- ExtendedData.pdf