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Review

Immunogenicity and efficacy of COVID-19 vaccines in people living with HIV: a systematic review and meta-analysis

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Objectives: Available data show that COVID-19 vaccines may be less effective in people living with HIV (PLWH) who are at increased risk for severe COVID-19. This meta-analysis aimed to compare the immunogenicity and efficacy of COVID-19 vaccines in PLWH with healthy individuals.

Methods: Pubmed/Medline, EMBASE, and the Cochrane Library were searched. Risk ratios of seroconversion were separately pooled using random-effects meta-analysis, and a systematic review without meta-analysis of SARS-CoV-2 antibody titer levels was performed after the first and second doses of a COVID-19 vaccine.

Results: A total of 22 studies with 6522 subjects met the inclusion criteria. After the first vaccine dose, seroconversion in PLWH was comparable to that in healthy individuals. After a second dose, seroconversion was slightly lower in PLWH compared with healthy controls, and antibody titers did not seem to be significantly affected or reduced among participants of both groups.

Conclusion: COVID-19 vaccines show favorable immunogenicity and efficacy in PLWH. A second dose is associated with consistently improved seroconversion, although it is slightly lower in PLWH than in healthy individuals. Additional strategies, such as a booster vaccination with messenger RNA COVID-19 vaccines, might improve seroprotection for these patients.

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Introduction

The transmission of SARS-CoV-2 has led to the ongoing global COVID-19 pandemic. By August 19, 2022, more than 590 million have had confirmed COVID-19 and more than 6 million have died worldwide (World Health Organization, 2022). The morbidity and mortality from COVID-19 and its complications and large-scale economic disruption have prompted an unprecedented pace in highly efficacious vaccine development (Berlin et al., 2020; Merad et al., 2022). As of August 19, 2022, a total of 12.4 billion vaccine doses have been administered (World Health Organization, 2022), and the most widely used are messenger RNA (mRNA) vaccines, including BNT162b2 (Pfizer-BioNTech, New York, NY, USA-Mainz, Germany) and mRNA-1273 (Moderna, Cambridge, MA, USA) vaccines and viral vector vaccines, such as Ad26.Cov2.S (Johnson & Johnson, New Brunswick, NJ, USA), ChAdOx (AstraZeneca, Cambridge, UK), Sputnik V (Gamaleya Research Institute of Epidemiology and Microbiology, Moscow, Russia), and the traditional inactivated virus alum-adjuvanted candidate vaccine CoronaVac (Sinovac, Beijing, China) (Piccaluga et al., 2022). All of these vaccines were well tolerated in clinical trials, and their proven efficacy was higher than 90% in preventing symptomatic laboratory-confirmed SARS-CoV-2 infection, except for the CoronaVac vaccine, which only had proven effectiveness of 51% (Baden et al., 2021; Kyriakidis et al., 2021; Mallapaty, 2021; Vergnes, 2021). High seroconversion rates were shown regardless of the class of vaccine used or previous infection status (Eyre et al., 2021).

Vaccine trials, however, did not report data about people living with HIV (PLWH) groups separately, leading to a paucity of data on the efficacy and safety of vaccines in the PLWH groups.

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These patients, who comprise only a small minority of the global population, are of particular interest because of possible suppression of reactivation of the immune system attributable to the primary disease or concurrent treatment (Lee et al., 2022). Data are urgently needed on PLWH because infection and viral shedding have been reported to be more severe and persistent in this group (Cederwall and Pålman, 2020; Couch et al., 1997; Manuel and Estabrook, 2019). PLWH are at increased risk for COVID-19-related complications and death (Silveira et al., 2021; Ssentongo et al., 2021).

Studies have shown variable efficacy of other vaccines, such as influenza and hepatitis B virus (HBV) vaccines, which is thought to depend on factors such as vaccine type and concurrent drugs, in the PLWH groups. In a meta-analysis on the immunogenicity of influenza vaccination in PLWH, trivalent inactivated influenza vaccines are effective in preventing influenza infection in PLWH (Remschmidt et al., 2014). In another meta-analysis, a double dose of the HBV vaccine and multiple injections were associated with better immune responses than the standard HBV vaccine regimen in PLWH, and higher seroconversion rates were observed in PLWH with high clusters of differentiation (CD 4+) T-cell levels, suggesting that PLWH should receive HBV vaccine as soon as possible after HIV diagnosis (Tian et al., 2021). HIV is characterized by attenuated humoral immunity that may reduce the efficacy of vaccines in PLWH, and there are major gaps in knowledge on the efficacy of COVID-19 vaccines in PLWH, especially in the context of all the knowledge about the efficacy of other vaccines in this population (Oyelade et al., 2022).

There are some meta-analyses now in a preprint on the immunogenicity of COVID-19 vaccines in PLWH cohorts, but a systematic exploration of related factors is still lacking. In this meta-analysis, we compared seroconversion rates and antibody titer levels for different COVID-19 vaccines between PLWH and healthy controls.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Page et al., 2021), and a review protocol (CRD420222356167) with search strategy was registered in the International Prospective Register of Systematic Reviews.

Search strategy

A comprehensive electronic search (from December 1, 2020 to August 10, 2022) of PubMed/Medline, EMBASE, and the Cochrane Library was conducted for articles published. No language restrictions were imposed. To improve the validity of data, we excluded non-peer-reviewed articles in preprint databases. The reference lists of all included articles were also hand searched to identify any potentially eligible studies.

We used a two-stage approach for screening: first, by title and abstract and then, by full-text article. Two researchers (JY and CW) independently screened each title, abstract, and full text. Data were crosschecked, and any discrepancies were resolved by discussion or consultation with a third independent investigator (XS). Studies were limited to human participants and of any follow-up duration and time points.

Inclusion and exclusion criteria

We performed a meta-analysis of prospective studies that met the following criteria: included human participants who received a COVID-19 vaccine of any brand and type, people living with HIV/AIDS, studies that included and reported data on a control group comprising individuals who are not infected with HIV, and studies that reported at least one seroconversion after COVID-19 vaccination or serological titers after COVID-19 vaccination.

We excluded studies that enrolled but did not report outcomes of a control group; reported seroconversion data in a form that prevented the calculation of proportions, risk of seroconversion, or the number of seroconverted participants; and reported serological titers in a form from which neither mean nor median titers could be derived.

When studies did not provide available data, we contacted the corresponding authors through email for information. We excluded studies only if data were not provided at the time of meta-analysis.

In light of the emergence of clinical studies on a third dose of COVID-19 vaccine in PLWH, we made a post hoc amendment to include studies reporting these data for qualitative analysis, prospective observational or experimental studies that involved human participants, all of whom should be receiving a COVID-19 vaccine of any brand and type, studies that involved people living with HIV/AIDS, and studies that reported seroconversion rates of PLWH with or without the inclusion of a control group.

Data extraction

Two researchers (JY and CW) synthesized data from all eligible studies and created graphs using a Microsoft Excel spreadsheet. At the end of the data extraction phase, all key extracted data were reviewed and quality checked by the same two researchers.

Data on study characteristics comprised setting, primary and secondary outcomes, study design, sample size, dropout and non-response rates, and inclusion and exclusion criteria. Participant data comprised age, sex, and disease and treatment history, including immunosuppressive regimen. Intervention-related data included vaccine type and brand, dosing schedule, number of participants receiving each type and brand of vaccine, and median or mean interval between doses. Outcome-related data comprised assay type, antibody measured, method of measurement, intervals of sample collection, and number of measurements.

Quality assessment

The risk of bias in nonrandomized studies of interventions tool was used to rate the risk of bias for nonrandomized included studies. This tool assesses seven domains: risk of bias from confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results (Lee et al., 2022). Two investigators (JY and CW) independently judged these domains as low, moderate, serious, or critical risk of bias or no information. All discrepancies were first discussed between the investigators, then split by a third investigator (XS) in case of persistent discordance. A study would be judged as having an overall low risk of bias if all the domains were judged as low risk. A study would be considered as having critical risk of bias if one domain was judged to be at high risk of bias. Assessment for publication bias was qualitative, through visual inspection for funnel plot asymmetry (Egger et al., 1997).

A standardized method, namely, version 2 of the Cochrane risk of bias tool was used for randomized trials (Sterne et al., 2019). During this study, however, no eligible randomized studies were found.

Data analysis

The primary outcomes of interest were seroconversion after a first and second dose of the COVID-19 vaccine. As brand and type
of assay, type of immunoglobulin (Ig), and definition of seroconversion differed across studies, Table 1 reports the respective data for each included study.

As the type of antibodies measured and reported differed across studies, Supplementary Tables 1 and 2 show the titers after a first and second vaccine dose, respectively. The time points of serological assessment after COVID-19 vaccination and the different brands of serological kits are shown in Table 1. We used a random-effects model to estimate the pooled risk ratios (RRs) and corresponding 95% confidence intervals (CIs) for the primary outcomes of interest. An RR < 1 indicates that PLWH had a lower risk of achieving seroconversion after COVID-19 vaccination than the control groups. Statistical heterogeneity of the results in the enrolled studies was assessed by the chi-squared test and I² statistic. We considered heterogeneity to be significant when the P-value < 0.05 or the I² statistic was ≥ 50% (Higgins and Thompson, 2002).

We performed subgroup analyses to determine if the results were influenced by the types of COVID-19 vaccine.

Because the SARS-CoV-2 antibody titer levels cannot be amenable to statistical pooling due to different methods and assays used, secondary outcomes were assessed using the synthesis review without a meta-analysis approach.

We performed separate meta-analyses for the RR of seroconversion (measured as RR compared with healthy controls) after each vaccine dose. Mixed-effects models were used to pool the logit transformed proportions of PLWH who achieved seroconversion after a first and second COVID-19 vaccine dose.

Statistical analyses were performed using RevMan 5.4 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020). The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (Guyatt et al., 2008).

Results

Study selection and characteristics

The selection procedure is summarized in Figure 1. Overall, 22 studies were included in the meta-analysis of seroconversion rates (Table 1) (Antinori et al., 2022; Bergman et al., 2021; Brumme et al., 2022; Feng et al., 2022; Frater et al., 2021; Heftdal et al., 2022; Huang et al., 2022; Jedicke et al., 2022; Khan et al., 2021; Levy et al., 2021; Lombardi et al., 2022; Lv et al., 2021; Madhi et al., 2021; Madhi et al., 2022; Netto et al., 2022; Ogbe et al., 2022; Rahav et al., 2021; Schmidt et al., 2022; Tuan et al., 2022; Woldemeskil et al., 2021; Zeng et al., 2022; Zou et al., 2022). Tables S1 and S2 present the serological antibody titers after a first and second dose of COVID-19 vaccines, respectively. In addition, one study that met the inclusion criteria for the meta-analysis was excluded because seroconversion rates among healthy controls could not be obtained in time from the corresponding authors (González de Aledo et al., 2022).

Of the 22 included studies, 10 (45%) used mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), six (27%) inactivated vaccines CoronaVac (Sinovac, Biotech) and BBIBP-CorV (SinoPharm-Beijing BBIBP-CorV), five (23%) studies involving viral vector vaccines AZD1222 (ChAdOx1 nCoV-19; Oxford-AstraZeneca) and Ad26.COV2.S (Janssen/Johnson & Johnson), and one (5%) recombinant spike protein nanoparticle vaccine co-formulated with a saponin-based adjuvant Matrix-M (NVX-CoV2373; Novavax; Gaithersburg, MD, USA). In one study, BNT162b2, mRNA-1273, and AZD1222 were used simultaneously (Brumme et al., 2022). Among the viral vector vaccines, AZD1222 was used in four (18%) studies (Brumme et al., 2022; Frater et al., 2021; Madhi et al., 2021; Ogbe et al., 2022) and as the sole vaccine in three (14%) (Frater et al., 2021; Madhi et al., 2021; Ogbe et al., 2022), and Ad26.COV2.S was used in only one (5%) study (Khan et al., 2021). Therefore, AZD1222 featured more prominently.

Vaccine response

Seven studies reported seroconversion after a first vaccine dose in PLWH (n = 603) compared with healthy controls (n = 884). There was no difference in the seroconversion rate between PLWH and healthy controls (RR 0.95, 95% CI 0.89-1.03, I² = 86%, Figure 2) (moderate certainty of the evidence).

In 20 studies with a total of 2068 PLWH and 4454 healthy controls, seroconversion rates were lower among the PLWH than the healthy controls after a second vaccine dose (RR 0.92, 95% CI 0.87-0.97, I² = 92%, Figure 3) (moderate certainty of the evidence).

Antibody titers did not seem to be significantly affected or reduced among participants after a second vaccine dose, with Lombardi et al. (2022) reporting a 0.44-fold reduction among eight healthy controls (median 1077 U/ml, interquartile range [IQR] 702-7551 U/ml) compared with 62 PLWH (median 2437 U/ml, IQR 1485-4526 U/ml) and Netto et al. (2022) reporting a 0.64-fold reduction among 204 PLWH (median 48.7 AU/ml, IQR 26.6-88.2 AU/ml) compared with 274 controls (median 75.2 AU/ml, IQR 50.3-112.0 AU/ml).

Heterogeneity in PLWH after the first and second doses

A subgroup analysis was performed for studies involving only mRNA vaccines and only non-mRNA vaccines after the first and second doses. After the first dose, there were no significant differences (P-value = 0.92 for test of subgroup effect; Figure 4) in the effects on seroconversion between mRNA vaccines (RR 0.87, 95% CI 0.60-1.27) and non-mRNA vaccines (RR 0.85, 95% CI 0.66-1.11). After the second dose, no significant differences (P-value = 0.03 for test of subgroup effect, Figure 5) were found in the effects on seroconversion between mRNA vaccines (RR 0.96, 95% CI 0.92-1.01) and non-mRNA vaccines (RR 0.84, 95% CI 0.76-0.93).

A sensitivity analysis was conducted according to the study- and patient-level categorical characteristics to account for heterogeneity in seroconversion observed after the first and second doses of COVID-19 vaccine. When studies of PLWH including inactivated virus vaccines or PLWH receiving antiretroviral therapy (ART) were excluded, a subgroup analysis was performed for studies involving noninactivated virus vaccines after both the first and the second dose. After the first dose, no significant difference was found in effects on seroconversion between PLWH and healthy controls (RR 0.98, 0.89-1.07, I² = 0%, Figure S1). After the second dose, there was a significant difference in the effects on seroconversion between PLWH and healthy controls (RR 0.92, 0.86-0.98, I² = 92%, Figure S2). Therefore, the COVID-19 vaccine platforms might be a confounder.

The brand of serology kit for assays and country/region of the study were of inconsistent significance across PLWH groups and are therefore unlikely to be major confounders overall.

The mixed-effects meta-regression of seroconversion against potential effect moderators (continuous and categorical study level characteristics), including mean age of patients, brand of serology kit, time points for assays after COVID-19 vaccination, and risk of bias of study, showed no consistent effect moderation across PLWH after both the first or the second dose.

All studies included in our meta-analysis involved healthy controls to improve comparability of data, and responses in healthy controls were homogenous across studies.
Table 1
Characteristics of included studies.

| Source            | Vaccine                        | n, Population(s) of interest | Age¹ | Gender¹ | Country/ Region | n, Comparison | Immunoassay                                                                 | Threshold for positive response | Endpoints of data collection |
|-------------------|--------------------------------|-----------------------------|------|---------|-----------------|---------------|----------------------------------------------------------------------------|-------------------------------|-----------------------------|
| Zou et al. (2022) | WIBP-CoV (inactivated)        | 46, HIV patients            | 36   |          | China           | 38, healthy controls | The serum levels of nAbs against the S protein RBD determined by SARS-CoV-2 nAbs assay kit by surrogate virus neutralization test (Zhuhai Livzon Diagnostics Inc, Zhuhai, China) | Positive serology: RBD: ≥ 10 BAU/ml | Day 28 after 2nd dose         |
| Zeng et al.       | BIBP-CoV or CoronaVac (inactivated) | 132, HIV patients        | 32   |          | China           | 130, healthy controls | S-RBD-IgG detected by magnetic particle chemiluminescence kits (Shengxiang Biotechnology, Changsha, China) | Positive serology: RBD: ≥ 1.0 | Day 28 and 180 after 2nd dose |
| Madhi et al. (2022)| NVX-CoV2373 (recombinant protein nanoparticle) | 122, HIV patients        | 39   |          | South Africa    | 2089, healthy controls | Anti-S-IgG antibodies                                                                 | Positive serology: > 95% participants in the placebo group | Day 14 after 2nd dose          |
| Huang et al. (2022)| Sinopharm and SinoVac CoronaVac (inactivated) | 129, HIV patients        | 34   |          | China           | 53, healthy controls | SARS-CoV-2 specific total antibody and S-IgG antibodies using Chemiluminescence assay (CLIA) kits (Beijing Wantai Biological Pharmacy Enterprise Co., Ltd., Beijing, China) | Positive serology: > 30 pg/ml | Day 15-28 after 2nd dose      |
| Antinori et al.  | BNT162b2 or mRNA-1273 (mRNA)  | 166, HIV patients          | 55   |          | Italy            | 169, healthy controls | The SARS-CoV-2 specific anti-N, and the anti-S/RBD tests (ARCHITECT SARS-CoV-2 IgG, and ARCHITECT SARS-CoV-2 IgG II) Quantitative, Abbott Laboratories, Wiesbaden, Germany respectively) | Positive serology: nAb ≥10 | Day 28 after 2nd dose          |
| Lombardi et al.  | mRNA-1273 (mRNA)              | 71, HIV patients           | 47   |          | Italy            | 10, healthy controls | Electrochemiluminescent Immuno Assay (ECLIA)                                                                 | Not explicitly stated         | Day 28 from first dose and day 28 after 2nd dose 7-155 days after the second dose (median of 37 days for people living with HIV and 26 days for controls) |
| Schmidt et al.   | BNT162b2 (mRNA)               | 50, HIV patients           | 55   |          | Germany         | 60, healthy controls | CE certified commercial ELISA (Euroimmun, Lübeck, Germany)                                                                 | Positive serology: RBD: > 1.1 | Day 42 and day 182 after 2nd dose |
| Ogbe et al. (2022)| AZD1222 (Viral vector)        | 54, HIV patients           | 42.5 |          | UK              | 60, healthy controls | Standardized total IgG ELISA against trimeric SARS-CoV-2 S protein                                                                 | Seropositive: >3-fold increase | Day 42 from first dose, and at 1 and 3 months after 2nd dose |
| Brunone et al.   | BNT162b2, mRNA-1273, AZD1222 (Viral vector) | 100, HIV patients        | 54   |          | Canada          | 152, healthy controls | Electrochemiluminescence sandwich immunoassays                                                                 | Not explicitly stated         | One month after the first dose, and at 1 and 3 months after 2nd dose |
| Hefdal et al.    | BNT162b2 (mRNA)               | 269, HIV patients          | 56.0 |          | Denmark         | 538, healthy controls | An in-house ELISA that detects IgG antibodies against the RBD of SARS-CoV-2                                                                 | Positive serology: >150 AU/ml | Three weeks and 2 months after the first dose |

(continued on next page)
| Source                  | Vaccine                  | n, Population(s) of interest | Age | Gender | Country/Region | n, Comparison | Immunoassay                                                                 | Threshold for positive response | Endpoints of data collection |
|------------------------|--------------------------|-----------------------------|-----|--------|----------------|---------------|-----------------------------------------------------------------------------|-------------------------------|-------------------------------|
| Feng et al. (2022)     | BIBP-CorV (inactivated)  | 42, HIV patients            |     |        | China          | 28, healthy controls | An in-house ELISA that detects IgG antibodies against the RBD of SARS-CoV-2 | Seropositive: >3-fold increase | Four weeks after the first dose and 4 weeks after 2nd dose |
| Khan et al. (2021)     | Ad26.Cov2.S (Viral vector) | 8, HIV patients            |     |        | South African  | 24, healthy controls | ImmunoSAFE COVID-19 Array Slides (Sengenics Corporation, Singapore) to measure the anti-SARS-CoV-2 IgG antibodies against SARS-CoV-2 N | The mean plus 2 SD of pre-pandemic control signal | Sixteen weeks after the first dose |
| Lv et al. (2022)       | CoronaVac (inactivated)  | 24, HIV patients            |     |        | China          | 24, healthy controls | A competitive ELISA kit to measure anti-SARS-CoV-2 neutralization antibodies | Not explicitly stated         | About 40 days after 2nd dose   |
| Tuan et al. (2022)     | BNT162.b2 (mRNA)         | 45, HIV patients            |     |        | USA            | 23, healthy controls | Healgen (Houston, TX, USA) COVID-19 anti-S-1gG/IgM Rapid Test Cassette       | Not explicitly stated         | Three weeks after the first dose (and prior to receipt of the second dose) and at 2-3 weeks after 2nd dose |
| Bergman et al. (2021)  | BNT162.b2 (mRNA)         | 90, HIV patients            |     |        | Sweden         | 90, healthy controls | Quantitative Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay              | Positive serology: > 0.79 U/ml | Twenty-four days after 2nd dose |
| Netto et al. (2022)    | CoronaVac (inactivated)  | 215, HIV patients           |     |        | Brazil         | 296, healthy controls | IgG antibodies targeting S1 and 2 proteins in the receptor binding domain (Indirect ELISA, LIAISON SARS-CoV-2 S1/S2 IgG, DiaSorin, Italy), and the virusNAb detection assay SARS-CoV-2 sVNT RBD-HRP Kit (GenScript, Piscataway, NJ, USA) | Positive serology: > 15.0 AI/μl | Six weeks (day 69) after 2nd dose |
| Frater et al. (2021)   | AZD1222 (Viral vector)   | 54, HIV patients            |     |        | UK             | 50, healthy controls | Standardized total IgG ELISA against trimeric SARS-CoV-2 S protein           | Not explicitly stated         | Days 42 and 56 after 2nd dose  |
| Rahav et al. (2021)    | BNT162.b2 (mRNA)         | 156, HIV patients           |     |        | Israel         | 272, healthy controls | VSV-S SARS-CoV-2 pseudo-virus neutralization assay (Gert Zimmer) ELISA (QuantVac; Euroimmun, Lübeck, Germany) | Positive serology: RBD: > 1.1 | Thirty days after 2nd dose |
| Jedicke et al. (2022)  | BNT162.b2 (mRNA)         | 88, HIV patients            |     |        | Germany        | 41, healthy controls | ELISA (QuantVacc; Euroimmun, Lübeck, Germany) | Not explicitly stated | Mean of 18.7 days (range 0-42 days) after the first and 35 days (range 1-128 days) after the boost vaccination. Two-three weeks following 2nd dose |
| Levy et al. (2021)     | BNT162.b2 (mRNA)         | 143, HIV patients           |     |        | Israel         | 261, healthy controls | ELISA that detects IgG antibodies against the RBD of SARS-CoV-2              | Positive serology: > 1.1       | Two-three weeks following 2nd dose |

(continued on next page)
Table 1 (continued)

| Source                  | Vaccine          | n, Population(s) of interest | Age$^{a}$ | Gender$^{b}$ | Country/Region | n, Comparison | Immunoassay                      | Threshold for positive response | Endpoints of data collection |
|-------------------------|------------------|-----------------------------|-----------|--------------|----------------|---------------|----------------------------------|--------------------------------|-------------------------------|
| Madhi et al. (2021)     | AZD1222 (Viral vector) | 52, HIV patients           | Patients: 37 (32-45) Controls: 34 (23-41) | Patients: 16/52 (31%)/Controls: 17/29 (39%) | South Africa | 29, healthy controls | Singleplex bead-based immunoassays were developed on the Luminex platform to quantitatively measure serum IgG binding to fibroblast-like synoviocytes and RBD | Seropositive: ≥2-fold increase | Day 28 from first dose and 14 days post booster |
| Woldemeskel et al. (2021) | BNT162,b2 (mRNA) | 12, HIV patients           | Patients: Median (range): 52 (25-59) Controls: Median (range): 41 (24-59) | Patients: 5/12 (41.7%)/Controls: 10/17 (58.8%) | USA       | 17, healthy controls | Euroimmun Anti-SARS-CoV-2 IgG ELISA | Not stated                     | Between 7 and 17 days after 2nd dose |

Abbreviations: BAU, binding antibody units; ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin; IQR, interquartile range; nAb, neutralizing antibodies; N, nucleocapsid; RBD, receptor binding domain; S, spike.
$^{a}$ Reported as median (IQR) unless otherwise stated.
$^{b}$ Reported as percentage of males unless otherwise stated.

![Figure 1. Flowchart of study selection.](image-url)
Quality assessment

A total of 20 (91%) studies were assessed to be at low risk of bias and two (9%) at moderate risk of bias (Table S3). No studies were considered to be at severe or critical risk of bias. The risk of bias was mainly associated with confounding effects, with controls not being age-matched or with recruited patients lacking available data at predetermined end points. The publication bias evaluation results showed that the funnel plot was generally symmetrical by visual inspection. Therefore, no significant publication bias was found in our study (Figure S3).

Discussion

This review is the first to assess and compare the efficacy of COVID-19 vaccines available at present in PLWH compared to the general population. In this systematic review and meta-analysis of 22 studies, we found that PLWH had a slightly lower seroconversion after a first and second dose of COVID-19 vaccine than healthy controls. The pooled RR for seroconversion after the first vaccine dose was lower among PLWH than healthy controls; however, there was no statistical significance between the two groups (RR 0.95, 95% CI 0.89-1.03, I² = 86%). Antibody response among PLWH improved significantly after the second dose (86.4%), but the response of the control group was more pronounced (92.2%). Therefore, the pooled RR after the second dose decreased to 0.92 among PLWH. Although the seroconversion was slightly lower after the first dose among PLWH than healthy controls, the immune response to COVID-19 vaccines was shown to be preserved after the second dose, which is consistent with one previous research (Lee et al., 2022). Hyperviremia may lead to a shortened half-life of the COVID-19 vaccines, which is why the subpopulations of PLWH may require repeated vaccination (Oyelade et al., 2022). The benefits of additional doses and boosters of vaccines are well established, both for COVID-19 (Doria-Rose et al., 2021; Livingston, 2021; Voysey et al., 2021) and for pre-existing vaccines, such as pneumococcal vaccine (Duarte et al., 2022) and inactivated Hantaan virus vaccine (Hantavax®) (Song et al., 2020). Our findings similarly highlight the importance of a second dose of the COVID-19 vaccine for PLWH. Across the included studies, a second dose of the COVID-19 vaccine was associated with greatly improved seroconversion and antibody titer levels, with increasing immunogenicity and protection in PLWH.

Among PLWH, our results show no ideal but favorable seroconversion rate, even after a second dose of COVID-19 vaccine, prompting the requirement for additional measures (e.g., booster vaccination). Lapointe et al. showed that in PLWH, the humoral response after the third dose greatly exceeded the level after the second dose, especially for the mRNA-1273 vaccine (Moderna, Cambridge, MA, USA) (Lapointe et al., 2022). In an observational study, Barda et al. (2021) showed that a third dose of the BNT162b2 vaccine was effective in protecting individuals against severe COVID-19-related outcomes, compared with receiving only two doses at least 5 months before. In August 2021, the US Food and Drug Administration approved a third dose of Pfizer-BioNTech and Moderna vaccines for PLWH populations, with other countries following suit (Wise, 2021).

Our meta-analyses show significant heterogeneity in immunogenicity between different PLWH groups after both the first and the second dose of COVID-19 vaccines. After the vaccination, the response noticeably varied in PLWH, which may be attributed to the diversity of anti-HIV drugs, or the widespread COVID-19 vac-

![Table](image-url)
citations resulted from the release of a multisociety joint statement advocating vaccination for all PLWH midway through several of the reported studies (Mohammed et al., 2020). Vaccine regimes should be tailored according to the kinds of anti-HIV drugs and the disease severity. One of the included studies found that robust humoral immunity was triggered in the majority of PLWH receiving ART after a full BNT162b2 vaccination; however, controls who were HIV-negative produced significantly higher mean anti-spike IgG concentrations with less variability (Jedicke et al., 2022).

Currently, there is no international consensus on the measures to determine immunogenicity. Surrogate measures, including seroconversion rates and geometric mean titers, were reported by many trials. These surrogate measures involved parameters related to recombinant 2019-nCoV spike, receptor binding domain, or neutralizing IgG or total antibodies. The use of immunomarkers to predict protection against COVID-19 has been the subject of debate (Earle et al., 2021; Garcia-Beltran et al., 2021; Jin et al., 2021; Khoury et al., 2021; Roozendaal et al., 2021; Vidal et al., 2021). The neutralizing antibody level has more recently been recognized as a reliable predictor of protection against symptomatic COVID-19; however, the measures used in many studies varied. In this systematic review, only studies that compared measures of effect between PLWH and healthy controls were included.

There are various studies that compare the immunogenicity of other vaccines between PLW HIV/AIDS and healthy individuals. Studies have established that hepatitis B, influenza, and pneumococcal conjugate vaccines have lower response rates in PLWH, which makes it necessary to study COVID-19 vaccines in PLWH (Boey et al., 2021; Lee et al., 2020; Nunes et al., 2020; Pallikkuth et al., 2018; Whitaker et al., 2012). In view of the HIV/AIDS spec-
The effect of CD4 count reduction on immune response remains to be determined. Data on patients with PLWH are rare (Amodio et al., 2021). However, even patients with primary antibody deficiencies, such as combined variable immunodeficiency, have developed antispikes antibodies after COVID-19 vaccination (Delmonte et al., 2021; Hagan et al., 2021). Therefore, immunization against COVID-19 may be particularly important for all PLWH.

Over the last decade, mRNA has emerged as a promising platform for developing vaccines against infectious diseases and cancer (Pardi et al., 2018). Compared with traditional vaccines, such as live attenuated vaccines, inactivated virus vaccines, and protein subunit vaccines, mRNA vaccines have the advantages of versatility, rapid development, good safety profiles, and potent immunogenicity (Alberer et al., 2017; Corbett et al., 2020; de Jong et al., 2019; Feldman et al., 2019; Gay et al., 2018). Therefore, multiple
researchers and companies have chosen this platform to develop vaccines against COVID-19. It is difficult to directly compare seroconversion rates of the COVID-19 mRNA vaccines with more traditional, frequently used vaccines. In our study, no significant difference was found in a subgroup analysis of mRNA versus conventional vaccines in PLWH. A systematic review by Fan et al. (2021), which compared mRNA vaccines with conventional vaccines in patients without HIV, summarized the safety and efficacy of the three main COVID-19 vaccine platforms (mRNA, nonreplicating viral vector, inactivated) reported in phase III trials. In terms of vaccine safety, mRNA vaccines showed more relevance to serious adverse events than the other two vaccine platforms, but no solid evidence indicated that COVID-19 vaccines directly caused serious adverse events. A network meta-analysis suggests that the immune response to the influenza vaccine might not be as robust in PLWH, but they appear to benefit from vaccination (Zhang et al., 2018). These findings reflect the current situation with COVID-19 and vaccination.

This study has several limitations. First, most of the enrolled studies are observational, but two are randomized controlled trials. Factors that might influence the immune response to the vaccine, such as differences in study design and sample size, might not be controlled for between PLWH group and the healthy control group. In addition, our findings did not control for CD4+ T-cell count and ART treatment. To deal with this limitation, we performed subgroup analysis and found that there was no significant effect modification between studies with different designs. Second, in our study, the rate of seroconversion was pooled after the first and second doses of a COVID-19 vaccine. However, the seroconversion rate is an indicator of an immune response to a vaccine; it is only a proxy for the effects of the vaccine on infection rates and COVID-19 severity. Data on clinical efficacy endpoints, such as COVID-19 infection rates in vaccinated PLWH, are still lacking. Third, we did not check the different studies including the same patients (e.g., once as an intervention group and then as a control). Last, the results may be imbalanced because nine of the 17 publications enrolled were on BNT162b2. In addition, vaccine type might affect seroconversion rates after COVID-19 vaccination. However, because the studies included in this review predominantly used mRNA vaccines, the possible differential analyses were limited.

Conclusion

In conclusion, this meta-analysis shows that, COVID-19 vaccines show favorable immunogenicity and efficacy in PLWH compared with healthy individuals. A second dose was associated with consistently improved seroconversion; although, it is slightly lower in PLWH than in healthy individuals. Additional strategies, such as the administration of a third (booster) vaccination with mRNA COVID-19 vaccines, might improve seroprotection for these patients. Moreover, our results suggest that policymakers, health planners, and other stakeholders should encourage COVID-19 vaccine uptake by providing trusted information and addressing COVID-19 vaccine hesitancy in PLWH.

Declaration of competing interest

The authors have no competing interests to declare.

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Ethical approval statement

Not applicable.

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Author contributions

JY and YC contributed equally to this paper and are joint first authors. CW and XZ contributed equally to this paper and are joint last authors. JY, CW, and YC conceived and designed the study. JY and YC selected the articles and extracted data. JY and CW were responsible for statistical analysis. JY and YL wrote the first draft of the manuscript. CW, XZ, and YL provided advice at different stages. All authors approved the final version of the manuscript. JY is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.10.005.

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