

Immunogenicity, effectiveness, and safety of SARS-CoV-2 vaccination in people with HIV

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Objectives: People with HIV (PWH) experience a greater risk of morbidity and mortality following COVID-19 infection, and poorer immunological responses to several vaccines. We explored existing evidence regarding the immunogenicity, effectiveness, and safety of SARS-CoV-2 vaccines in PWH compared with controls.

Methods: We conducted a systematic search of electronic databases from January 2020 until June 2022, in addition to conference databases, to identify studies comparing clinical, immunogenicity, and safety in PWH and controls. We compared results between those with low (<350 cells/ μ l) and high (>350 cells/ μ l) CD4 $^{+}$ T-cell counts where possible. We performed a meta-analysis of seroconversion and neutralization responses to calculate a pooled risk ratio as the measure of effect.

Results: We identified 30 studies, including four reporting clinical effectiveness, 27 immunogenicity, and 12 reporting safety outcomes. PWH were 3% [risk ratio 0.97, 95% confidence interval (95% CI) 0.95–0.99] less likely to seroconvert and 5% less likely to demonstrate neutralization responses (risk ratio 0.95, 95% CI 0.91–0.99) following a primary vaccine schedule. Having a CD4 $^{+}$ T-cell count less than 350 cells/ μ l (risk ratio 0.91, 95% CI 0.83–0.99) compared with a CD4 $^{+}$ T-cell count more than 350 cells/ μ l, and receipt of a non-mRNA vaccine in PWH compared with controls (risk ratio 0.86, 95% CI 0.77–0.96) were associated with reduced seroconversion. Two studies reported worse clinical outcomes in PWH.

Conclusion: Although vaccines appear well tolerated in PWH, this group experience poorer immunological responses following vaccination than controls, particularly with non-mRNA vaccines and low CD4 $^{+}$ T-cell counts. PWH should be prioritized for mRNA COVID-19 vaccines, especially PWH with more advanced immunodeficiency.

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AIDS 2023, 37:1345–1360

Keywords: COVID-19 vaccines, HIV, SARS-CoV-2, seroconversion, vaccination response

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Received: 11 February 2023; revised: 29 March 2023; accepted: 6 April 2023.

DOI:10.1097/QAD.0000000000003579

Introduction

The SARS-CoV-2 pandemic, which emerged at the end of 2019, has led to significant morbidity, mortality, and social and economic disruption, globally. Moreover, the pandemic has had an unprecedented impact on health systems, including those affecting people with HIV (PWH), who experience disproportionately high levels of noninfectious comorbidities, which place them at a higher risk of adverse outcomes following SARS-CoV-2 infection [1]. PWH have reported changes in service provision, challenges in accessing care, and negative impacts on personal relationships, employment, and income due to COVID-19 [2,3].

PWH have an increased incidence of and worse clinical outcomes after several vaccine preventable infections compared with people without HIV, including influenza [4], pneumococcus [5], and hepatitis B [6,7]. They also have poorer magnitude and breadth of immunological responses following vaccination, and poorer durability of protection [8–10]. This likely relates to persistent immune dysfunction, exhaustion, and immune senescence due to HIV infection, which is only partially restored by antiretroviral therapy [11,12].

Although the magnitude of increased risk remains uncertain, several studies indicate that PWH are at a higher risk of severe illness, hospitalization, and death from COVID-19 than their uninfected peers, when adjusted for age, comorbidities, and sociodemographic factors [13–18]. More advanced immunosuppression and detectable viremia have been associated with poorer outcomes, while antiretroviral therapy appears protective [15,18,19]. Although the mechanisms remain unclear, intersecting social and structural determinants of health, older biological age, and greater frequency of age associated comorbidities are associated with worse outcomes for PWH with COVID-19 [19]. It is less clear whether PWH are at a higher risk of acquiring COVID-19, in the absence of additional risk factors, though it appears they may be at a higher risk of breakthrough infection following vaccination [20,21]. Taken together, these data support the prioritization of PWH for early SARS-CoV-2 vaccination across multiple international jurisdictions, to date.

Despite improvements in the understanding of COVID-19 therapeutics and development of monoclonal antibodies for the prevention and treatment of COVID-19, their activity and durability against contemporary variants appears limited [22,23]. In addition, continued physical distancing, social isolation, and mask wearing may be challenging. Hence, endogenous immunological responses, acquired through vaccination, remain central to COVID-19 prevention in vulnerable populations, including PWH. However, only a limited number of PWH were included in the original COVID-19 vaccine

licensing studies, and results from these small subpopulations of PWH were not published [24–29]. Several gaps in our understanding of COVID-19 vaccination in PWH remain, including the impact of CD4⁺ T-cell count on immunological responses in PWH. Therefore, we conducted a systematic review and meta-analysis of the existing literature, to better understand the efficacy, immunogenicity, and safety of vaccines to prevent SARS-CoV-2 infection in PWH versus people without HIV.

Materials and methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [30]. The protocol for this review was registered with the PROSPERO database (CRD42022340626). Ethics approval was not sought for this review, due to the incorporation and synthesis of only preexisting, published data.

Search strategy and selection criteria

We used OVID to search MEDLINE (PubMed) and EMBASE for eligible studies, published in the peer-reviewed literature, in the English language, between January 1, 2020, and June 16, 2022. We used medical subject headings (MeSH) and text words to identify studies reporting immunological, clinical, or safety outcomes from PWH and controls (Supplementary Tables 1 and 2, <http://links.lww.com/QAD/C873>, <http://links.lww.com/QAD/C874>). We searched online conference abstract databases for the International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention; the International AIDS Conference and the Conference on Retroviruses and Opportunistic Infections (CROI) from January 2020 until August 2022. We searched reference lists from selected papers and additional studies that met inclusion criteria. Two review authors (D.G., J. H., or J.M.) independently screened titles and abstracts of the references identified by the search using Covidence [31]. The authors independently assessed full texts of relevant titles and abstracts to identify studies that fulfilled inclusion criteria. Disagreements were resolved through discussion between authors (D.G., J. H.) and in case of nonconsensus by consulting with an additional review author (J.M.). All randomized, and observational clinical and laboratory studies, conducted with human participants over the age of 16 years, comparing outcomes in people with HIV infection and controls (nonimmunocompromised people without HIV) who had received two doses of SARS-CoV-2 vaccination were eligible for inclusion. Case reports, case series, and studies investigating outcomes post one or three doses of vaccine, or without a comparator arm were excluded.

Data extraction and outcomes

We extracted relevant data from included studies, using a customized data extraction tool (Microsoft Excel) (D.G.), and the study team subsequently reviewed these at the end of the extraction phase (J.H., J.M.). The data extracted included publication year, author, country, study design, sample size, SARS-CoV-2 vaccine type, and dosing schedule. Participant data extracted included age, sex, antiretroviral therapy use, CD4⁺ T-cell count, and HIV viral load at the time of vaccination. Outcome data extracted included the proportion of participants with a detectable response and magnitude of that response for SARS-CoV-2 specific antibodies, SARS-CoV-2 neutralization, and SARS-CoV-2 specific T-cell responses. Where more than one publication contained data from a single cohort of patients, data could be combined from these publications for the outcomes of interest. Per-protocol efficacy and safety outcomes, including local and systemic reactions, were extracted and summarized narratively.

Given the small number of studies reporting on immunological outcomes stratified by CD4⁺ T-cell count, we contacted study authors directly to obtain results stratified by high and low CD4⁺ T-cell count strata, if not already reported.

Meta-analysis

Data for meta-analysis were extracted into RevMan [Review Manager (Computer program) Version 5.4. The Cochrane Collaboration, 2020]. Risk ratios were calculated to quantify the proportion of participants with SARS-CoV-2 seroconversion and detectable neutralizing antibody (nAb) responses. These immune outcomes were selected due to their importance as correlates of clinical protection [32,33], while estimates of magnitude, T-cell responses, efficacy, and safety outcomes were summarized descriptively due to the small number of studies reporting these outcomes and the heterogeneity of the outcome measures used. A meta-analysis determined a pooled effect risk ratio, using a random effects model. Risk ratios were expressed with a 95% confidence interval (95% CI), and study heterogeneity was assessed using the I^2 statistic (with I^2 values $\geq 50\%$ considered as 'substantial heterogeneity'). If the statistical heterogeneity was significant, then a random-effects model (the Mantel-Haenszel method) was selected. Sub-group meta-analyses were performed for SARS-CoV-2 seroconversion for vaccine subtypes in studies (mRNA, non-mRNA), and CD4⁺ T-cell count strata (high versus low).

Risk of bias assessment

Two reviewers (D.G., R.P.M.) independently assessed the risk of bias. In case of any discrepancy, a third reviewer was consulted (J.H., J.M.). We used the Cochrane risk bias assessment tool for randomized controlled trials (RCTs), RoB2, including randomization processes, allocation concealment, blinding, and outcome

measurement and reporting to assess the risk of bias in RCTs [34]. We assessed the risk of bias for non-randomized studies using the Newcastle-Ottawa Scale (NOS), which included an assessment of confounding, selection bias, classification bias, measurement bias, missing data, and reporting [35].

Results

From the search, 46 articles were identified for full text review, and 30 studies were eligible for inclusion (Fig. 1) [21,36–64]. These included four studies reporting clinical outcomes [39,40,44,47]; 27 immunogenicity studies (23 publications [36–38,40,41,43,45–49,51–57,59–61,63,64], and four conference abstracts [42,50,58,62]), and 12 studies reporting safety outcomes [37,40,43,45,46,50,51,53,54,56,58,59]. Nine studies were from Asia [37,42,43,45,48,51,52,55,59], 10 from Europe [36,40,46,49,50,57,58,60,62,64], six from North America [21,41,44,47,61,63], three from Africa [39,53,54], and two were from South America [38,56]. One study was retrospective [21], five were cross-sectional [43,48,51,55,63], while 24 were prospective, including seven case-control studies [39,42,44,46,48,49,61], and two RCTs [53,54].

Immunogenicity

Humoral responses

Twenty-seven studies including 4451 PWH and 5984 controls, compared immunological outcomes following vaccination in PWH versus a control group. Twelve studies investigated immunological responses following a schedule of mRNA vaccines (mRNA-1273, or BNT162b2) [36,40,42,49,52,57–61,63,64], two adenoviral vector vaccines (ChAdOx1) [46,53], eight inactivated vaccines (BBIBP-CorV or CoronaVac) [37,38,43,45,48,51,55,56], one protein subunit vaccine (NVX-2373) [54], and four reported on cohorts who had received a variety of the above vaccines [41,62]. Of these, 23 studies reported on the proportion of participants with SARS-CoV-2 IgG seroconversion following vaccination, while 25 described an estimate of the magnitude of antibody response. Seventeen studies reported on SARS-CoV-2 neutralization [36,38,41,43,45,46,48,49,51–54,56,59,61–63], and six reported on SARS-CoV-2 specific T-cell responses [36,45,46,51,57,63].

Of the 23 studies reporting on seroconversion following two doses of SARS-CoV-2 vaccine, (Table 1, Fig. 2a), 2681 of 2898 PWH (92.5%) and 4383 of 4486 controls (97.7%) developed detectable antispike or anti-RBD IgG antibodies. The pooled risk ratio for seroconversion in PWH was 0.97 (95% CI 0.95–0.99; $I^2 = 84\%$, $P = 0.002$).

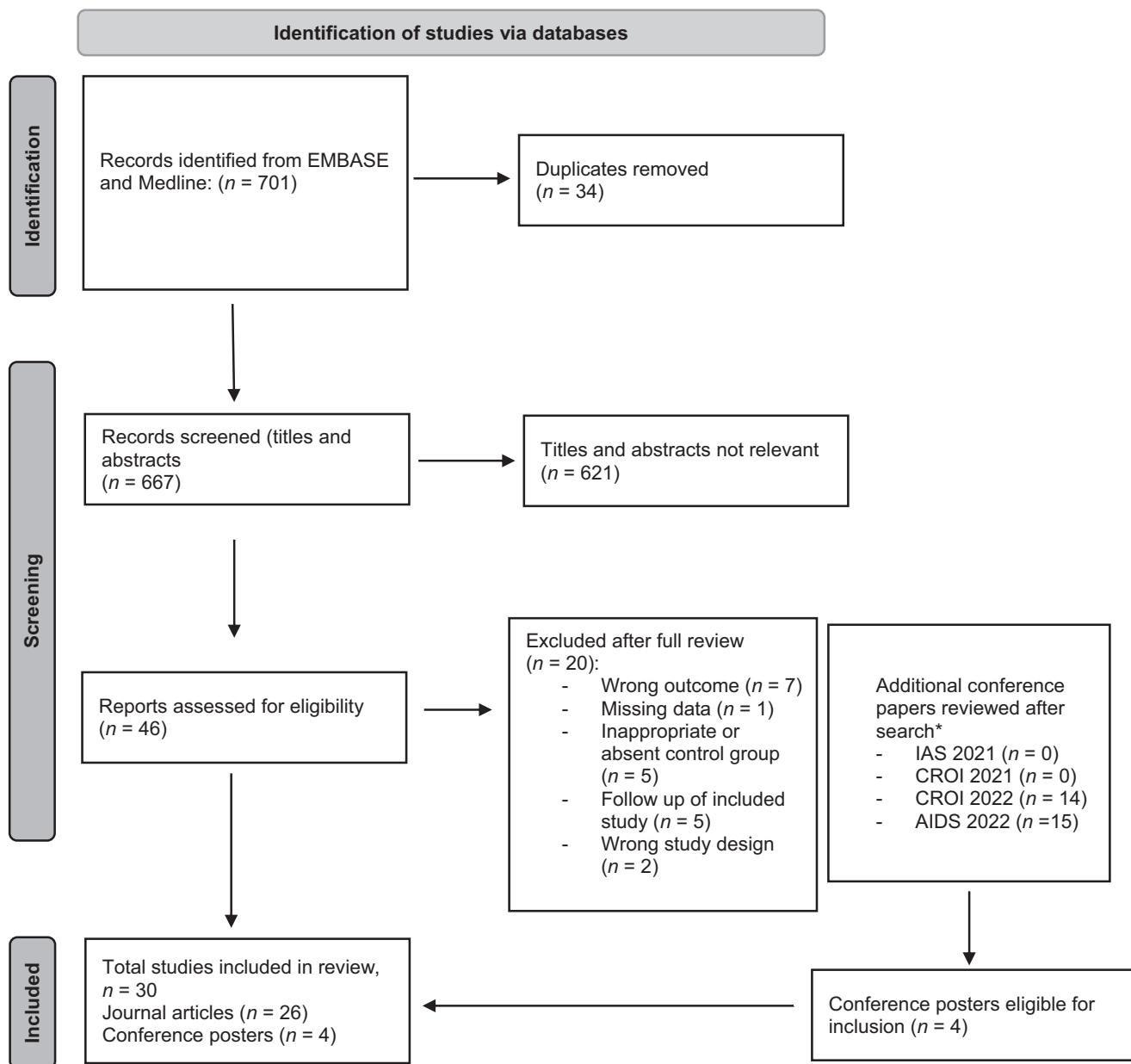


Fig. 1. PRISMA flow diagram for systematic review search strategy.

Similarly, in 15 studies reporting on nAb responses, a small but significant reduction in detectable nAb in PWH was found compared with controls. One thousand seven hundred and thirty-nine of 1992 (87.3%) PWH, and 3097 of 3407 (90.9%) of controls had a detectable neutralization response, with a pooled risk ratio in PWH of 0.95 (95% CI 0.91–0.99; $I^2 = 81\%$, $P = 0.02$) (Fig. 2b). The reporting of quantitative SARS-CoV-2 Spike IgG and neutralization responses was disparate between studies, meaning a combined estimate of magnitude of effect, could not be calculated for these outcomes. However, 21 of 25 studies reported a numerically lower magnitude of Spike IgG response, while eight of 10

studies reported numerically lower levels of neutralizing antibody in PWH than in controls (Table 1).

T-cell responses

Seven studies reported T-cell responses following vaccination in PWH and controls (Table 1) [36,38,45,46,51,57,63]. Interferon (IFN)-gamma release, in response to spike peptide stimulation of T lymphocytes, increased sequentially post doses one and two of mRNA vaccine in PWH [36]. However, median IFN-gamma release was significantly lower if CD4⁺ T-cell count was less than 200 cells/ μ l compared with more than 500 cells/ μ l. Similarly, Balcels *et al.* [38] observed a

Table 1. Summary of immunological outcomes following second dose vaccine in people with HIV versus healthy controls in included studies.

Study details	Author, journal or conference, Year, Ref.	Country	Vaccines	Study design	Population		Immunological outcomes				T cell responses	
							Seroconversion (n , %); summary estimate		Neutralization (n , %); summary estimate			
					PWH (n); mean or median age (years); CD4 ⁺ cell count (cells/ μ l)	Control (n); mean or median age (years)	PWH	Controls	PWH	Controls		
Antinori, et al. Clinical Infectious Diseases, 2022 [36]	Italy	Two mRNA vaccines (57% received BNT162b2 and 70 (43%) received mRNA-1273	Prospective Cohort Study (unmatched)	166; NR; 80.7%; CD4 > 200	169; NR	155/160 (96.9%); NR	168/168 (100%); Median 23.53 BAU/ml (1378–3758)	133/153 (86.9%)	72/73 (98.6%); NR	NR	Median IFN- γ 343 (IQR 188–715) pg/ml; IL2 177 (IQR 87–304) pg/ml	
Ao, et al. Emerging Microbes and Infections, 2022 [37]	China	Two inactivated vaccines; BBIBP-CorV or CoronaVac	Prospective Cohort Study (unmatched)	139; 155 (range 23–81); NR	120; 54; range 21–83	121/139 (87.1%); 134.2 (114.0–158.0)	119/120 (99.2%); GMT (95% CI) (95% CI) 317.5 (267.1–377.4)	NR	NR	NR	NR	
Balelli, et al. Clinical Infectious Diseases, 2022 [38]	Chile	Two doses inactivated vaccine; Coronavac	Prospective Cohort Study (unmatched)	55; 46.8 (range 52); 358.8 (100.0)	65; 44.3 (range 51)	39/57 (70.1%); GM/C (15.98–28.13) RU/ml	60/65 (92.3%); GM/C (30.0–45.05) RU/ml	25/55 (45.5%); Median % inhibition 28.72 (IQR 15.74–54.13)	54/65 (83.1%); Median % inhibition 51.21 (IQR 34.6–68.6)	NR	NR	
Bekker, et al. Lancet, 2022 ^a [39]	South Africa	One x Ad26.COV2.S	Prospective Case-control Study (SHONKE)	39; 383; NR; NR	437/719; 42.0 (33.0–51.0)	NR	NR	NR	NR	NR	NR	
Bergman, et al. EBioMedicine, 2022 [40]; Xu, et al. AIDS, 2022 [66]	Sweden	Two mRNA vaccines; BNT162b2	Prospective single Centre Cohort Study (COVAXID)	90; 53.5 (42–63.25); 565 (280–722.5)	90; 54 (33–67.25)	78/79 (98.7%); Median 1.613 (IQR 897–2643) U/ml	78/78 (100%); Median 21.92 (IQR 13.98–365.1) U/ml	NR	NR	NR	NR	
Brumme, et al. NPJ Vaccines, 2022 [41]	Canada	Two doses of vaccine; BNT162b2, Moderna, or AZ mRNA-2 83% vs 97% Hebevirous 8% vs 2% AZ x 2 vs 1%	Prospective Cohort Study	100; 54 (40–61); 710 [525–935]	152 HC (59% HCw); 47 [35–70]	89/90 (98.9%); Median (IQR) 3.86 (3.63–4.07) log10 U/ml	90/91 (98.9%); Median (IQR) 3.97 (3.76–4.22) log10 U/ml	160 (IQR 40–320)	80 (IQR 40–160)	NR	NR	
Cai, et al. J Medical Virology, 2022 [43]	China	Two inactivated vaccines; Sinopharm, Sinovac, 24 mixed, Two mRNA vaccines or 1 J-I; BNT162b2 51%, mRNA-1273 42%, Ad26.COV2.S 7%	Prospective Matched -Case Control Study (CVET-II)	143; 32.55 ± 8.69; 398.96±202.31	50; 29.84±8.51	83/143 (58.0%); Mean (SD) 1.58 (1.19) S/CO	38/50 (76.0%); Mean (SD) 1.58 (2.33) S/CO	65/67 (97.0%)	19/20 (95.0%)	NR	NR	
Coburn, et al. JAMA Open Network, 2022 ^a [44]	USA	Two doses BNT162b2 51%, mRNA-1273 42%, Ad26.COV2.S 7%	Prospective Cohort Study (unmatched)	72; 636 (449–858)	NR	NR	NR	NR	NR	NR	NR	
Feng, et al. Clinical Medicine, 2022 [45]	China	Two doses BBIBP-CorV	Prospective Cohort Study (unmatched)	72; 639.0 +/- 221.9	42; 37.79 SD 8.804	24/42 (57.1%)	26/28 (92.9%)	29/42 (69.0%)	20/28 (71.4%)	CD4 ⁺ 0.04% (IQR 0.03–0.06%); CD8 ⁺ 0.08% (IQR 0.04–0.10%); Median 39/44 (89%); SFC/10 ⁶ PBMCs 337 (IQR 188–672)	CD4 ⁺ 0.062% (IQR 0.028–0.093%); CD8 ⁺ 0.09% (IQR 0.05%); Median 25/31 (81.0%); SFC/10 ⁶ PBMCs 340 (IQR 97–610)	
Fraer, et al. Lancet HIV, 2021 [46]	UK	Two doses ChAdOx1, 4–6 weeks apart	Prospective Case Control (COV002 trial)	104; 694.0 (573.5–859.5)	54; 38.5 (29.2–45.0)	NR; GMT 1025 (93.5% CI 774, 1356) EU/ml	13/15 (87%); Median FnRT50 75.0 (IQR 30.0–100.0)	NR	NR	NR	NR	
Haidar, et al. Clinical Infectious Diseases, 2022 [47]	USA	Two doses mRNA, ChAdOx1; single dose Ad26.COV2.S, mRNA-1273 (48.3% 61.4% 1273) or BNT162b2 vaccines (50.7% 64% 1271). Only 1.0% (13/1271) received an adenovirus vector vaccine Ad26.COV2.S (85% 11/13); ChAdOx1 nCoV-19, 15% 2/13)	Prospective Cohort Study (COVICS)	94; 57.4 (10.0); NR	127; 44.2 (13.3)	75/94 (79.8%); Median 6.87 (2.88–15.20) S/CO	118/127 (92.9%); Median 6.47 (3.12–11.69) S/CO	NR	NR	NR	NR	

Table 1 (continued)

Author, journal or conference, Year, Ref.	Country	Vaccines	Study design	Population		Immunological outcomes					
				PW/H (<i>n</i>): mean or median age (years); CD4 ⁺ cell count (cells/ μ m ³)		Seroconversion (<i>n</i> , %); summary estimate		Neutralization (<i>n</i> , %); summary estimate		T cell responses	
				Control (<i>n</i>), mean or median age (years)	PW/H	Controls	PW/H	Controls	PW/H	Controls	Controls
Han, et al. Infection and Drug Resistance, 2022 [48]	China	Two inactivated vaccines; BBIBP-CoV or Corona Vac	Cross-sectional Case-control Study (matched, age and sex)	47; 34 (IQR 26–42); 47.4 (range 145–92)	18; 37 (IQR 33–50)	7/10 (70.0%); GMT 9.15 S/CO, 95% CI 0.26–5.01 S/CO	8/18 (100%); GMT 19, 95% CI 16–23) S/CO	8/10 (80.0%); GMT 43, 95% CI 15–120	18/18 (100%); NR	NR	NR
Heitdal, et al. Journal Internal Medicine, 2021 [49]	Denmark	Two doses BNT162b2	Prospective Case-Control (Age-matched)	265; 56 (49–64); 640 (500–780)	538; 56 (49–63)	263/269 (97.7%); GMT 0.95% CI 20–442.13	536/538 (99.6%); GMT 171.05 (31,571.18–38,948.67)	263/269 (97.7%); NR	530/536 (98.8%); NR	NR	NR
Huang, et al. Viruses, 2022 [51]	China	At least one inactivated vaccine; BBIBP-CoV or CoronaVac	Cross-sectional Study	129; 34 (IQR 28–38); 63.0 (499.5–848.8)	53; 34 (range 29–47)	87/94 (92.6%); 28.9 (7.4–83.2)	51/51 (100%); 40.3 (28.5–71.6)	67/94 (71.3%); 42/51 (82.3%); GMT 24.0, 95% CI 14.0, 38.0.2	39/64 (60.9%); 42/51 (82.3%); GMT 23.4, 95% CI 4.0, 64.0	26/32 (81.3%); median 56.1 pg/ml (IQR 118.7)	26/32 (81.3%); median 91.5 pg/ml (IQR 31.1, 227.4)
Jedelcke, et al. HIV Medicine, 2021 [64]	Germany	Two doses of BNT162b2	Prospective Cohort Study	52; 53.5 (26–86); NR	41; 44 (range 23–61)	NR; Median 502.5 (IQR 118.8 RU/ml)	NR; Median 246.2 (IQR 218.7 RU/ml)	NR; Median 502.5 (IQR 118.8 RU/ml)	NR; Median 246.2 (IQR 218.7 RU/ml)	NR	NR
Levy, et al. Clinical microbiology and Infection, 2021 [52]	Israel	Two doses BNT162b2	Prospective Cohort Study	143; 49.8±11.6; mean 700 (95% CI 648–757); cells/ μ L (IQR 428–725)	261; 55.8±14.3	139/143 (97.2%); GMT 5.2 (95% CI 4.8–5.5) S/CO	258/261 (98.9%); GMT 6.1 (95% CI 5.8–6.4) S/CO	131/135 (97.0%); GMT 44.9, 95% CI 3.666–550.0	197/201 (98.0%); GMT 482.8 (95% CI 41.0–567.5)	NR	NR
Liu, et al. Vaccines, 2022 [55]	China	Two doses CoronaVac	Cross-sectional Study	55; 36±11; 57.8	21; 35±8	NR; Median 15.8 U/ml (IQR 10.4–23.3)	NR; Median 24.6 U/ml (IQR 11.3–23.2)	NR; Median 16 U/ml (IQR 11.3–23.2)	NR; Median 16 U/ml (IQR 11.3–23.2)	NR	NR
Madhi, et al. Lancet HIV, 2021 [53]	South Africa	Two doses ChAdOx-1	Multicentre, Double-Blind Placebo-Contaminated Randomised Controlled Trial (CV005)	37; 37 (32–45); 742 (540–933)	34; 34 (23–41)	28/32 (87.5%); median 34.7 (10.5–620.4) BAU/ml	22/23 (95.7%); median 34.2 (23.8–55.8) BAU/ml	17/18 (94.4%); ID50 151.5 (95% CI 95.8–419.0)	20/22 (90.9%); ID50 151.5 (95% CI 394.5–642.4)	NR	NR
Madhi, et al. Lancet HIV, 2022 [54]	South Africa	Two doses NVX-CoV2373	Randomized, Observer-Blinded, Multicenter, Placebo-controlled Phase 2A/B Trial (2019nCoV-501)	122; 390 (99); 729.5 (range: 80–2076)	2089; 31.5 (12.9)	58/58 (100%); GMT 1442.0 (95% CI 1063.0, 19,612.3) EU/ml	1226/1274 (96.2%); 30520.6 (95% CI 28687.9, 32,470.4) EU/ml	456/41 (73.8%); GMT 39.7 (95% EU/ml)	1059/1220 (86.8%); GMT 87.3 (95% EU/ml)	NR	NR
Netto, et al. Lancet HIV, 2022 [56]	Brazil	Two doses CoronaVac	Prospective Cohort Study (CoronaRheum)	215; 655 (458–900)	296; 48 (37–58)	185/204 (90.7%); GMT 48.7 (IQR 26.6–88.2) AU/ml	262/274 (96.7%); GMT 75.2 (IQR 50.3–112.0) AU/ml	143/202 (70.8%); median nAb activity 46.2%; (IQR 26.9–69.7)	229/274 (83.6%); median nAb activity 60.8%; (IQR 39.8–79.9)	NR	NR
Oyaert, et al. Frontiers in Immunology, 2022 [57]	Belgium	Two doses BNT162b2	Prospective Cohort Study	27; 47 (30–66); 254 (128–346)	54; 37 (17–63)	23/23 (100%); Median 3,140 (range 200–22,400) BAU/ml	52/52 (100%); Median 3,140 (range 200–22,400) BAU/ml	NR	17/25 (68.0%); 67.4–25,400 BAU/ml	45/51 (88.2%); 67.4–25,400 BAU/ml	45/51 (88.2%); 67.4–25,400 BAU/ml
Rahav, et al. Clinical Medicine, 2021 [58]	Israel	Two doses BNT162b2	Prospective Cohort Study	156; 49.0 (42.0–57.0); 700 (NR)	272; 57.0 (44.0–67.0)	154/156 (98.7%); GMT 5.14 (95% CI 4.84–5.46)	269/272 (98.9%); GMT 5.98 (95% CI 5.70–6.28)	NR; GMT 467.60 (95% CI 382.5–571.7)	NR; GMT 474.0 (95% CI 403.2–557.3)	NR	NR
Schmidt, et al. Viruses, 2022 [60]	Germany	Two doses BNT162b2	Prospective Cohort Study	50; 55 (46–60); 634 (370–906)	60; 42 (30–53)	50/50 (100%); Median Extinction ratio 8.0 (IQR 7.2–8.8)	60/60 (100%); Median Extinction ratio 8.6 (IQR 7.2–9.5)	18/60 (30.0%); NR	18/60 (30.0%); NR	NR	NR

Table 1 (continued)

Study details	Author, journal or conference, Year, Ref.	Country	Vaccines	Study design	Population			Immunological outcomes			T cell responses
					PWH (n); mean or median age (years); CD4 ⁺ cell count (cells/ μ l)	Control (n); mean or median age (years)	PWH	Seroconversion (n, %); summary estimate	Controls	PWH	
Spinelli, et al. Clinical Infectious Diseases, 2022 [61]	USA	Two doses mRNA Vaccine	Case-control Study (matched sex, age, and vaccine)	100; 59 (52–66); 511 (351–796)	100; 59 (52–66)	88/100 (88.0%); Geometric mean ratio to HC 0.57 (95% CI 0.36–0.88)	95/100 (95.0%); NR	76/100 (76.0%); Geometric mean ratio to HC 0.76 (95% CI 0.49–1.19)	88/100 (88.0%)	NR	NR
Sun, et al. JAMA Internal Medicine, 2022 ^a [21]	USA	At least one dose of SARS-CoV-2 vaccine	Retrospective Cohort Study	8536; 51 (37–60); NR	629211; 51 (33–66)	NR	NR	NR	NR	NR	NR
Woldemekel, et al. Clinical Infectious Diseases, 2022 [63]	USA	Two doses BNT162b2	Cross-sectional Observational Study	12; 52 (45.8–56.8); 913 (range of 649–1678)	17; NR	11/11 (100.0%); median 8.84 RU/ml (IQR NR)	17/17 (100.0%); median 9.49 RU/ml (IQR NR)	12/12 (100.0%); NR	19/19 (100.0%); NR	10/10 (100.0%)	15/15 (100.0%)
Witkop, et al. CROI, 2022 [62]	France	Two doses of BNT162b2 (93% in PWH vs. 87% in controls), mRNA-1273 (6.0 vs. 7.7%), ChAdOx1-Sincov-19 (0.7 vs. 3.6%), Three PWH and 15 controls received heterologous prime-boost vaccination.	Prospective Cohort Study	754; NR (50–61); NR (70% had CD4 ⁺ cell counts above 500 cells/ μ l)	720; 50 (39–60)	732/754 (97.1%); GMT 1151 BAU/ml (95% CI 1076–1232)	719/754 (95.7%); GMT 1337 (95% CI 1251–1428) BAU/ml	712/720 (98.9%); CI 145.9; 173.91	712/720 (98.9%); CI 250.2–295.4	NR	NR
Fideli, et al. CROI 2022/ Portillo, et al. Frontiers in Immunology, 2022 [58]	Switzerland	Two mRNA vaccines (PWH: 40.5%; BNT162b2: 59.5%; mRNA 1273: HCs 100%; mRNA 1273)	Prospective Cohort Study (CCVAC/HIV)	102; 54 (47.0–65.0); 602 (45.5–83.5)	49; 30 (No IQR)	124/124 (100.0%); GMT 2372.01 RU/ml (95% CI 2192.3–2566.4)	48/48 (100.0%); GMT 2815.6 RU/ml (95% CI 2677.9–2960.3)	NR	NR	NR	NR
Hensley, et al. CROI 2022/ PLoS Med 2022. [50]	Netherlands	Two doses mRNA; ChAdOx1; single dose Ad26.COV2.S; mRNA-1273 (PWH 100, 8.7%; HCs 247, 56.1%) or BNT162b2 vaccines (884, 76.6%; 94.21.49%); Ad26.COV2.S (20, 1.7%); 73, 16.6%.	Prospective Cohort Study	1154; NR (994, 86.1% < 65 years); NR (426, 96.8% < 65 years); 1113 (96.4%); CD4 > 250	440; NR (994, 86.1% < 65 years); NR (426, 96.8% < 65 years); 1113 (96.4%); CD4 > 250	NR; GMC 1060 BAU/ml (95% CI NR)	NR; GMC 1585 BAU/ml (95% CI NR)	NR	NR	NR	NR
Rajasuriar, et al. AIDS 2022 [42]	Malaysia	Two x BNT162b2	Prospective Case-control (age-matched controls)	68; 37.2 (33.3–42.5); 554 (361–790)	52; 37.3 (30.1–43.2)	68/68 (100.0%); NR	51/51 (100.0%); NR	NR	NR	NR	NR

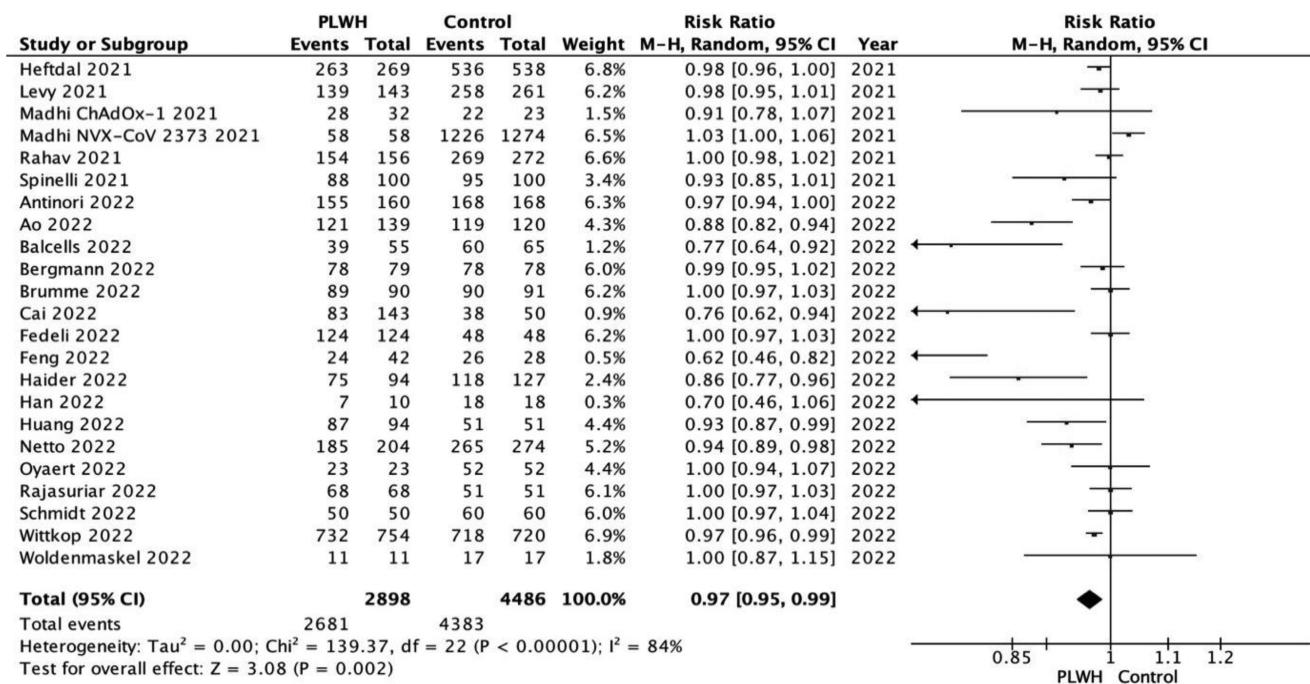
AU, arbitrary units; BAU, Basic Arbitrary Units; CROI, Conference of Retroviruses and Opportunistic Infections; EU, ELISA units; GMC, Geometric mean concentration; GMT, geometric mean titer; HC, healthy controls; HCW, healthcare workers; IQR, interquartile range; IU, international units; NR, not reported; PBMC, peripheral blood mononuclear cell; PWH, people with HIV; RU, relative units; S/CO, signal to cutoff (ratio); SFC, Spot forming cells.

^aClinical effectiveness reported in study.

^bProportion of Spike-protein specific IFN- γ secreting T cells measured by flow cytometry.

^cProportion with cellular immune responses measured by QuantIFERON Sars-CoV-2 interferon gamma release assay.

(a) Seroconversion responses



(b) Neutralisation responses

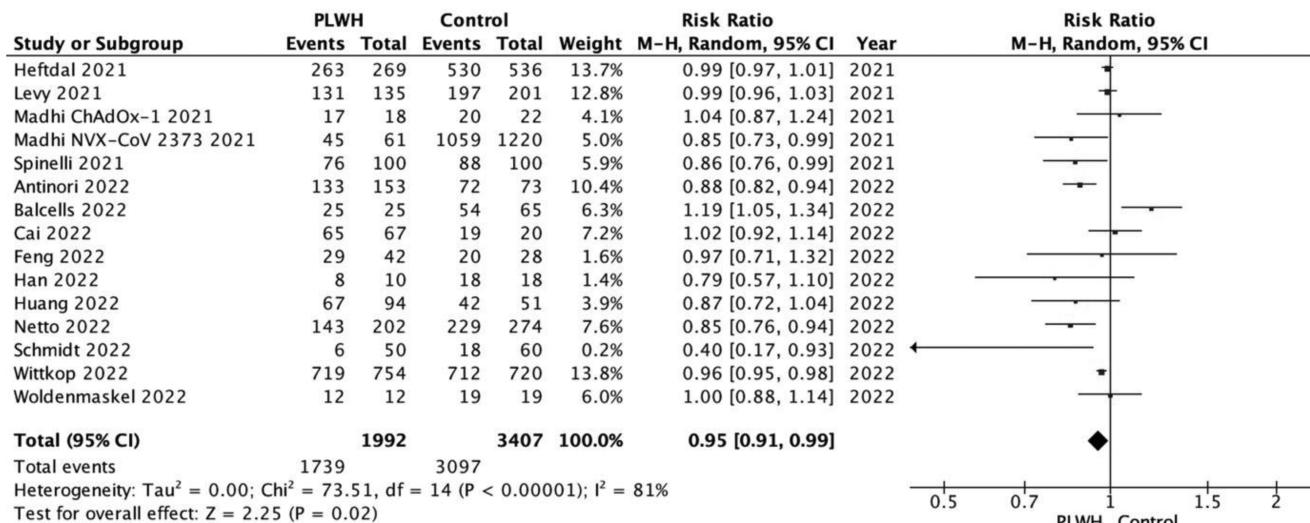


Fig. 2. Forest plot comparing (a) seroconversion and (b) neutralization response in people living with HIV versus healthy controls 2–8 weeks following dose two of all COVID-19 vaccinations. The squares represent the effect estimates from individual studies, the size of the square being proportional to the weight of the study. The horizontal lines represent the 95% confidence interval of the study estimate. The black diamond represents the pooled effect size.

trend towards reduced IFN-gamma and IL-4 responses to SARS-CoV-2 multimer peptides in PWH CD4⁺ T-cell count less than 500 cells/ μ l after two doses of CoronaVac, but these did not reach statistical significance.

In a cohort of virologically suppressed PWH with median 694 CD4⁺ T cells/ μ l, IFN gamma responses were

comparable with HIV-negative controls following ChAdOx1 vaccination [46]. Similarly, Feng *et al.* [45] demonstrated that CD4⁺ and CD8⁺ T-cell activation was comparable between PWH and controls, and did not correlate with CD4:CD8 T-cell ratios. However, their study excluded patients with CD4⁺ T-cell count less than 200 cells/ μ l [45]. Two smaller studies did not find

significant differences between PWH and controls in T lymphocyte responses following mRNA vaccines [57,63]. In contrast, Huang *et al.* [51] reported that PWH with robust CD4⁺ T-cell counts had significantly lower responses than controls on a commercial IFN-gamma release assay, following inactivated COVID-19 vaccines after adjusting for age, sex, comorbid disease, vaccine type, and vaccine interval.

Subgroup analyses

Ten studies comparing responses between PWH and controls also stratified immunological responses by CD4⁺ T-cell count (Table 2) [36,37,40,42,47,48,50,51,55,56]. Only one study stratified T-cell responses by CD4⁺ T-cell count [36], and four studies stratified neutralization responses [36,42,48,56].

Antinori *et al.* [36] reported that PWH with CD4⁺ T-cell count less than 200 cells/ μ l were less likely to develop SARS-CoV-2 nAb than those with CD4⁺ T-cell count 200–500 and more than 500 cells/ μ L, and had a significantly lower neutralization titer than those with CD4⁺ T-cell count more than 500 cells/ μ L. In contrast, Rajasuriar *et al.* [42] did not observe a difference in neutralization activity, for either the D146G ancestral or Omicron BA.1 variant, but it was reduced against the delta variant in the group with CD4⁺ T-cell count less than 800 cells/ μ l when compared with controls. Similarly, Han *et al.* [48] found that nAb titers were significantly lower in PWH with CD4⁺ T-cell count 350 cells/ μ l or less, compared with higher CD4⁺ T-cell counts. Similarly, PWH with CD4⁺ T-cell count less than 500 cells/ μ l who received CoronaVac were less likely to develop nAb, and had lower neutralizing activity than both PWH with CD4⁺ T cells at least 500 cells/ μ l and controls. This remained significant in multivariable models adjusting for age and sex [56].

In seven studies reporting on seroconversion responses, a small, but significant reduction in detectable anti-Spike antibodies was seen in those with CD4⁺ T-cell counts less than 350 cells/ μ l, compared with higher CD4⁺ T-cell counts; 208 of 246 (84.5%) CD4⁺ T-cell count less than 350 cells/ μ l, and 1572 of 1644 (95.6%) of those with higher CD4⁺ T-cell counts had detectable seroconversion. The pooled risk ratio for detectable seroconversion in PWH was 0.91 (95% CI 0.83–0.99; $I^2=65\%$, $P=0.01$) (Fig. 3a). The difference in neutralization did not reach significance in the three included studies (Fig. 3b). When compared with controls, PWH with a CD4⁺ T-cell count less than 350 cells/ μ l had a 15% reduction in seroconversion following two doses of any COVID-19 vaccine, while those with CD4⁺ T-cell count more than 350 cells/ μ l had a 3% reduction. However, this did not reach statistical significance in the six included small studies (Figure S1, <http://links.lww.com/QAD/C870>). Notably, the study by Hensley *et al.* [50] did not report a proportion of controls with detectable antibodies

so was not included in these comparisons (CD4⁺ T-cell count < 350, or >350 cells/ μ l versus controls).

In 10 studies exploring seroconversion rates in those receiving mRNA vaccines, there was no significant difference between PWH and controls; the pooled risk ratio was 0.99 (95% CI 0.98–1.00, $I^2=0\%$, $P=0.01$) (Fig. 4a). In contrast, fewer PWH receiving nonmRNA vaccinations seroconverted relative to controls, pooled risk ratio 0.86 (95% CI 0.77–0.96, $I^2=94\%$, $P=0.008$) (Fig. 4b).

Clinical efficacy

Four studies, including 592 906 participants (72 595 PWH), reported on vaccine effectiveness following COVID-19 vaccination [39,40,44,47]. In a retrospective multicenter cohort study of 33 029 PWH engaged in care and 80 965 controls matched by age, sex, race/ethnicity, and sex at birth, the association between HIV status and breakthrough COVID-19 infection, after SARS-CoV-2 vaccination (93% mRNA) was explored [44]. Most participants were male (92%), virologically suppressed on antiretroviral therapy (91%), and at least 55 years old (70%). They reported a higher risk of breakthrough infection in PWH than the control group [adjusted hazard ratio (aHR) 1.28; 95% CI 1.19–1.37], after adjustment for demographic, clinical, and vaccine factors. The increased risk was not explained by either CD4⁺ T-cell count, or HIV viral load, but breakthrough was higher in the context of the delta variant. PWH receiving mRNA-1273 vaccination were 34% less likely to experience breakthrough infections than those in receipt of BNT162b2 (aHR 0.66, 95% CI 0.57–0.77), and 50% less likely after a third dose of mRNA-1273 (aHR 0.50, 95% CI 0.38–0.67).

The SISONKE study [39] assessed the effectiveness of a single dose of Ad26.COV2.S COVID-19 vaccine in South Africa. Here, healthcare workers (HCWs) were matched to unvaccinated controls, by age, sex, geographical location, number of risk factors for disease severity (including HIV status), and socioeconomic status. The primary outcome was the effectiveness of vaccination on COVID-19 related hospitalization, or death from 28 days following vaccination. The study included 477 102 HCWs, of whom 39 383 (8.3%) were PWH. The vaccine effectiveness for COVID-19-related hospital admission and critical or intensive care admission was comparable between PWH and HCW without HIV. However, although vaccination reduced mortality in cases and controls, vaccine effectiveness appeared reduced in PWH (65%, 95% CI 13–93), for COVID-19 related death, when compared with HCW without HIV (83%, 95% CI 72–97).

A prospective observational study, by Bergman *et al.* [40], included 90 PWH ($n=90$) receiving two doses of BNT162b vaccines and did not report any cases of

Table 2. Immunological outcomes stratified by CD4⁺ T-cell count in people with HIV in included studies.

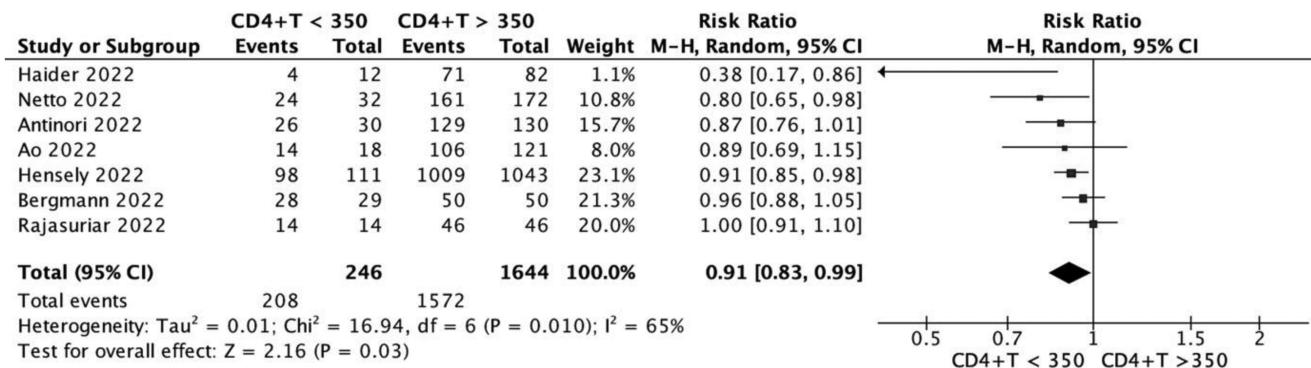
Author	CD4 ⁺ T-cell strata	Immunological outcomes			
		Seroconversion, (n/N, %)	Seroconversion summary estimate	Neutralization, (n/N, %)	Neutralization summary estimate ^a
Antinori, et al. ^b [36]	CD4 < 200	26/30 (86.7%)	507 BAU/ml (IQR 212–1143)	21/30 (70%)	30 (IQR 5–80)
	CD4 200–500	53/53 (100%)	1477 BAU/ml (IQR 471–2056)	45/51 (88.2%)	40 (IQR 10–160)
	CD4 > 500	76/77 (98.7%)	1782 BAU/ml (IQR 989–2769)	67/72 (93.1%)	80 (IQR 40–160)
	CD4 < 200	14/18 (77.8%)	GMT 82.49 (95% CI 53.2–128.0)	NR	NR
	CD4 200–500	62/74 (83.8%)	GMT 130.0 (95% CI 102.1–165.5)	NR	NR
	CD4 > 500	44/47 (93.6%)	GMT 170.0 (95% CI 133.7–216.4)	NR	NR
Bergmann, et al. Xu, et al. [40,66]	CD4 < 350	28/29 (96.6%)	Median (IQR) 1645 (606–2989)	NR	NR
	CD4 > 350	50/50 (100%)	Median (IQR) 1613 (925–2622)	NR	NR
	CD4 < 350	NR	NR – demonstrated graphically only	NR	NR
Han et al. ^b [48]	CD4 > 350	NR	NR	NR – demonstrated graphically only	NR
	CD4 < 200	4/12 (33.3%)	NR	NR	NR
Haidar et al. ^a [47]	CD4 < 200	71/82 (86.6%)	NR	NR	NR
	CD4 > 500	NR	NR	NR	NR
Huang et al. ^b [51]	CD4 > 500	NR	NR	NR	NR
	CD4 ≥ 500	NR	NR	NR	NR
Liu, et al. ^b [55]	CD4 > 350	11.2 U/ml (IQR, 4.6–21.2)	NR	NR	NR
	CD4 < 350	22.4 U/ml (IQR, 17–24.4)	NR	NR	NR
Netto et al. ^b [56]	CD4 > 350	GMT 42.6 AU/ml (IQR 22.9–68.9)	20/31 (65%)	Median 41.6% (IQR 20.8–64.6)	NR
	CD4 < 350	GMT 53.3 AU/ml (IQR 30.2–92.4)	123/171 (72%)	Median 49.9% (IQR 30.6–73.1)	NR
Hensley et al. ^b [50]	CD4 < 350	98/111 (88.2%)	GMC 611 BAU/ml (95% CI 427–876)	NR	NR
	CD4 > 350	1009/1043 (96.7%)	GMC 1129 BAU/ml (95% CI 1043–1222)	NR	Inhibition titer median (IQR) 1667.71 (1194.04–2767.76) (IU/ml)
	CD4 > 350	14/14 (100%)	All individuals achieved the assay's upper limit of detection, >250 IU/ml	46/46 (100%)	Inhibition titer median (IQR) 1615.38 (913.88–2325.22) (IU/ml)
Rajasuriar et al. ^b [42]	CD4 < 350	Unable to be determined; 43 individuals achieved the assay's upper limit of detection, >250 IU/ml	NR	NR	NR
	CD4 > 350	46/46 (100%)	NR	NR	NR

AU, arbitrary units; BAU, Basic Arbitrary Units; GMC, Geometric mean concentration; GMT, geometric mean titer; IQR, interquartile range; NR, not reported; PWH, people with HIV; SD, standard deviation.

^aDilutional titer; no units.

^bStudy demonstrates statistically significant association between CD4⁺ T-cell count and immunological response ($P < 0.05$).

(a) Seroconversion response



(b) Neutralisation response

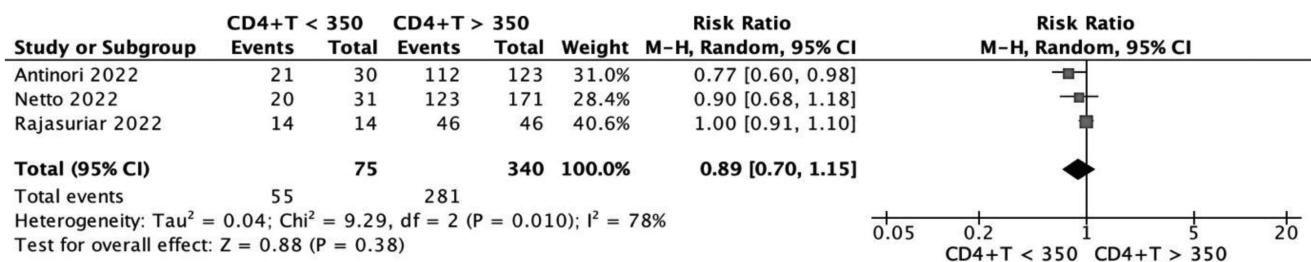


Fig. 3. Forest plot comparing (a) seroconversion and (b) neutralization response in people living with HIV with CD4⁺ T-cell counts <350 versus >350 cells/ μ l, 2–8 weeks following the second dose of all COVID-19 vaccinations. The squares represent the effect estimates from individual studies, the size of the square being proportional to the weight of the study. The horizontal lines represent the 95% confidence interval of the study estimate. The black diamond represents the pooled effect size. For the studies by Haider *et al.* and Antinori *et al.* [36], responses were stratified by CD4⁺ T-cell counts <200 versus >200 cells/ μ l.

COVID-19 in these participants. Similarly, there was a single breakthrough infection in the study by Haider *et al.* [47] in a PWH with CD4⁺ T-cell count less than 200 cells/ μ l. However, these studies were limited by their sample size and underpowered to make conclusions about vaccine efficacy in the PWH group. None of the vaccine efficacy studies systematically tested participants living with HIV or controls for COVID infection in the absence of symptoms.

Safety

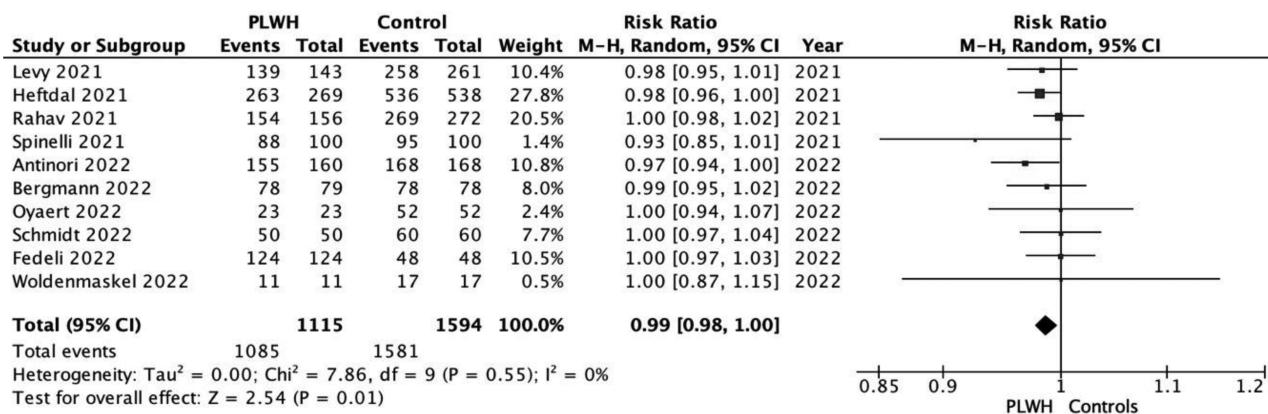
Twelve studies compared vaccine safety in PWH versus controls [37,40,43,45,46,51,53,54,56,58,59,65]. One prospective observational study found that the overall incidence of adverse events, dominated by localized reactions (e.g. pain, swelling, redness), was comparable between PWH (12.9%) and healthy controls (13.3%) [37]. Pain was the most frequent adverse event, reported by 8.6% PWH versus 7.5% of controls, while systemic adverse events, including rash, fatigue, or drowsiness occurred infrequently overall. Importantly all adverse events were mild (grade 1 or 2), occurred within 7 days of vaccination, and resolved spontaneously within 7 days. Cai *et al.* [43] and Huang *et al.* [51] observed comparable safety outcomes. In a study by Bergman *et al.*

[40] that included 90 PWH receiving two doses of BNT162b2 vaccine and several other immunocompromised groups, PWH were not more likely than the control group to have local or systemic adverse events. In fact, PWH had numerically fewer adverse events than several other immunocompromised groups. Two small studies did not observe any adverse events in vaccinated people [45,46].

Following ChAdOx1 administration, PWH experienced frequent, mild adverse events, at similar rates to HIV-negative controls. For example, 75 and 47.1% of individuals reported localized reactions following prime and boost doses, respectively, with injection site pain being most common. In contrast, systemic reactions, dominated by headache and fatigue, occurred in 75.5 and 43.1%, respectively, and were significantly less frequent following second dose in PWH than in controls [46].

Importantly, COVID-19 vaccination has a limited impact on important HIV parameters. HIV viral blips and virological failure were rare after vaccine administration [52], though the proportion of PWH with undetectable viral loads increased in two studies [45,66]. No opportunistic infection events were reported, although

(a) mRNA vaccine



(b) Non-mRNA vaccine

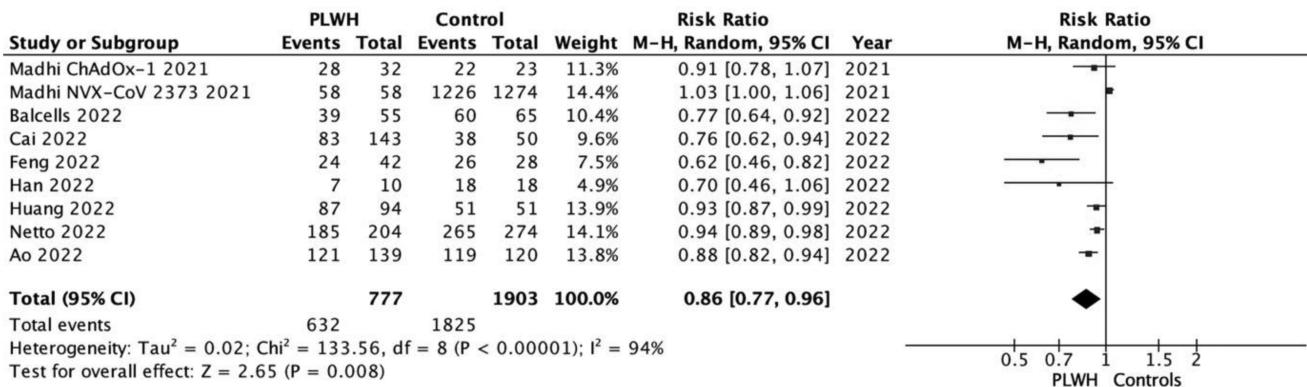


Fig. 4. Forest plot comparing seroconversion in people with HIV versus controls in participants receiving (a) mRNA vaccines and (b) non-mRNA vaccines, 2–8 weeks following the second dose of all COVID-19 vaccinations. The squares represent the effect estimates from individual studies, the size of the square being proportional to the weight of the study. The horizontal lines represent the 95% confidence interval of the study estimate. The black diamond represents the pooled effect size.

two studies demonstrated an overall reduction in T-cell count postvaccination, with preservation of CD4:CD8 ratio [45,52]. In contrast, Han *et al.* [48] observed an increase in CD4⁺ T-cell count and CD4:CD8 ratio, but reduction in CD8⁺ T-cell count after vaccination.

Risk of bias assessment

Two RCTs were assessed for bias, using the Cochrane RoB2 assessment tool. This indicated a low risk of bias in included RCTs (Figure S2, <http://links.lww.com/QAD/C871>). Cohort and case-control studies were assessed for bias using the NOS with predetermined criteria (Table S3, <http://links.lww.com/QAD/C875>). Twenty-four of these observational studies achieved scores of at least 6 (Table S4, <http://links.lww.com/QAD/C876>). Higher quality cohort studies generally scored better in comparability criteria, and included more appropriate control groups. Funnel plots for both seroconversion and neutralization responses in PWH (Figure S3a, b, <http://links.lww.com/QAD/C872>) were asymmetrical, potentially indicating true heterogeneity, reporting or methodological biases, or chance [65].

Discussion

This systematic review and meta-analysis identified 30 studies including a large number of PWH reporting on clinical effectiveness, safety, and immunogenicity of two doses of COVID-19 vaccine in PWH compared with people without HIV. All studies were observational except for two RCTs. Importantly, COVID-19 vaccines appeared well tolerated in PWH.

SARS-CoV-2 seroconversion in PWH was high, ranging from 57.1 to 100%. A meta-analysis demonstrated a 3% reduction in the detection of seroconversion following vaccination in PWH compared with controls. However, failure to seroconvert was more common in PWH with CD4⁺ T-cell counts less than 350 cells/ μ l, who had a 9 and 15% reduction in seroconversion compared with PWH with higher CD4⁺ T-cell counts and healthy controls, respectively. In contrast, the presence of detectable neutralization responses was more variable, between 11 and 100% for PWH and 30–100% for controls. Nevertheless, in this meta-analysis, we

demonstrated a 5% reduction in the detection of nAb response in PWH versus healthy controls. Although the difference in neutralization response appeared more prominent (11%) in those with CD4⁺ T-cell counts less than 350 cells/ μ l versus PWH with higher CD4⁺ T-cell counts, this did not reach significance, likely due to the small number of studies eligible for analysis. Certainly, several other studies, not eligible for inclusion in this analysis, have demonstrated a reduction in humoral responses in PWH with low CD4⁺ T-cell counts, following COVID-19 vaccination [67–70]. However, humoral responses in PWH are not diminished to the same magnitude as some other immunocompromised host groups [40,47,57,59].

T-cell responses were reported heterogeneously across seven studies, which precluded the calculation of a pooled estimate. Four studies reported numerically lower T-cell responses, reflected in reduced T-cell activation, in PWH versus controls. This reduction was most evident in those with lower versus higher CD4⁺ T-cell counts across several studies.

Although few studies explore vaccine effectiveness in PWH, the available data suggest that these poorer immunological responses translate to poorer clinical outcomes, and are consistent with data that levels of neutralizing antibodies and total antispike IgG are correlates of clinical protection from COVID-19 [32,33]. Coburn *et al.* [44] highlighted that PWH experienced approximately 28% more breakthrough infections following mRNA vaccination than their HIV-negative controls, and that this risk was 34% higher in those with CD4⁺ T-cell counts less than 200 cells/ μ l, compared with PWH with CD4⁺ T-cell counts at least 500 cells/ μ l after adjustment for vaccine type, clinical, and demographic factors. This finding is also consistent with previous experience with influenza [71], hepatitis B [72], and pneumococcal [73] vaccines [9,10] in PWH, indicative of both poorer initial response and shorter durability of immunological responses [8], and more breakthrough infections. Moreover, lower CD4⁺ T-cell count at time of vaccination, and higher HIV RNA levels in plasma have been frequently associated with poorer humoral responses to other vaccines [74–77]. Of particular concern, the SISONKE study of adenoviral vector vaccination in South African HCWs demonstrated that the protective effect of COVID-19 vaccination against COVID-19-related death in PWH was reduced when compared with controls. Although the mechanism for a higher likelihood of worse outcomes remains unclear, it is likely related to the intersection of the additional risk of age-associated and other comorbidities experienced by PWH, social determinants, and HIV-specific factors [78]. PWH experience a greater burden of traditional risk factors for severe COVID-19, including age, diabetes, cardiovascular disease, and obesity [1,16,19]. Higher proportion of black and minority

ethnicities, and social deprivation scores were associated with an increased risk of mortality in PWH in the OpenSAFELY study [13]. HIV-related factors, including access to ART, virological suppression and lower CD4⁺ T-cell count have been associated with poorer outcomes following COVID-19 in PWH [15,79]. Despite ART, PWH experience persistent immune dysregulation, inflammation, and immunosenescence that likely contributes to suboptimal immunological responses to vaccines [12,80–82]. Hence, alternative dosing, boosting, and adjuvant strategies that have been explored for some vaccines for PWH may be important for COVID-19 vaccines also [71,83,84].

A systematic review, recently published by others, explored antibody responses in PWH following COVID-19 vaccination and demonstrated similarly high rates of seroconversion in PWH and controls [85]. However, this previous review included studies with and without control groups, evaluated responses following both one and two doses of vaccination, and did not calculate a pooled estimate of effect. Our study includes additional meta-analyses of immunological outcomes with stratification by CD4⁺ T-cell count, and also includes a narrative review of clinical and safety outcomes.

Further studies are needed to better characterize immunological responses to SARS-CoV-2 vaccination in PWH. Of particular interest should be the ascertainment of factors associated with nonresponse to primary and booster doses of vaccination, the humoral and cellular immune responses toward contemporary circulating variants following vaccination, and the intersection between vaccine responses and immunological responses following infection. Well designed prospective studies of additional and sequential booster doses of COVID-19 vaccination are needed to understand their immunogenicity, safety, and real-world effectiveness in PWH, especially in those with more advanced immunosuppression (e.g. CD4⁺ cell counts \leq 350/ μ l) and in the context of contemporary circulating variants. Although our study indicates that those with CD4⁺ T-cell count less than 350 cells/ μ l have reduced humoral responses, this threshold warrants further delineation. This will enable the optimization of vaccination schedules for the prevention of breakthrough COVID-19, hospitalization, and death in PWH.

Although this is the first published systematic review and meta-analysis to compare the effectiveness, safety, and immunogenicity of COVID-19 vaccines in PWH and controls, our study has several limitations. Heterogeneity among eligible studies was substantial as evident in our meta-analyses, which likely reflects differences in study design, laboratory assays, and the selection and reporting of outcomes. The review included studies using disparate definitions of immunogenicity (seroconversion, neutralization, and T-cell responses), and collected different

adverse events as measures of clinical safety. Moreover, the use of different immunological assays, and presentation of these results with different units, meant determining a summary estimate of a magnitude of effect was not possible. Hence, we restricted meta-analysis to the dichotomous outcome of a detectable seroconversion or neutralizing antibody response per study protocol. Developing standardized and consistent methodologies and reporting units to assess humoral and cellular responses would assist in comparing immunological responses further. In addition, clinical outcomes were not commonly reported in PWH compared with controls and limited follow up beyond the two-dose schedule meant the longer-term effect of vaccination on subsequent COVID-19 infection could not be determined. Finally, the population of PWH in this study was mostly male, on ART, and virologically suppressed, which may limit generalizability to women living with HIV, and those PWH not yet on ART, including those recently diagnosed.

COVID-19 vaccines are well tolerated, and beneficial in PWH and are an essential tool to reduce COVID-related morbidity and mortality. However, PWH demonstrate reduced seroconversion and neutralization responses when compared with controls, and appear to experience more breakthrough infections, especially in the context of lower CD4⁺ T-cell counts. PWH should be prioritized for COVID-19 vaccination, especially with CD4⁺ T-cell counts less than 350 cells/ μ l with a preference for mRNA vaccines. Further studies are needed to optimize SARS-CoV-2 immunity and vaccination schedules in all PWH, with particular consideration for PWH with low CD4⁺ T-cell counts.

Acknowledgements

The authors would like to acknowledge Lorena Romero, Ian Potter Library, Alfred Hospital, Melbourne, Australia, for assistance with the search strategy, and the following for providing additional stratification of immune outcomes by CD4⁺ T-cell count strata: Dr Hong Ren and Colleagues, Department for Infectious Diseases, The Second Affiliated hospital of Chongqing Medical University. Dr Katie Hensley and colleagues, Erasmus Medical Centre, Rotterdam, Netherlands. A/Prof. Reena Rajasuriar and Colleagues, Centre of Excellence for Research in AIDS, Kuala Lumpur, Malaysia. Dr Xu, Dr Nowak and colleagues, Department of Infectious diseases, Karolinska University Hospital, Stockholm, Sweden

Study design – D.W.H.G., J.H.M., and J.F.H.

Literature search – D.W.H.G.

Titles and abstracts reviewed for inclusion – D.W.H.G., J.H.M., and J.F.H.

Data extraction – D.W.H.G.

Meta-analysis – D.W.H.G., R.P.M.

Risk of bias assessment – D.W.H.G., R.P.M.

Manuscript draft – D.W.H.G.

Manuscript review and approval – D.W.H.G., R.P.M., J.H.M., and J.F.H.

Conflicts of interest

J.H.M. is supported by the Medical Research Future Fund MRF2014921. J.F.H.'s institution received reimbursement for her participation in Advisory Boards for Gilead Sciences and ViiVHealthcare. All authors have no conflicts of interest to declare.

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