International Journal of Infectious Diseases 146 (2024) 107110

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Humoral response after mRNA COVID-19 primary vaccination and single booster dose in people living with HIV compared to controls: A French nationwide multicenter cohort study—ANRS0001s COV-POPART

Paul Loubet[1,2,3,*], Jean-Daniel Lelievre[4], Alexis François[5], Elisabeth Botelho-Nevers[6], Christian Chidiac[7,8], David Chirio[9], Vincent Dubee[10], Bertrand Dussol[11], Florence Galtier[12], Mojgan Hessamfar[13,14], Enkelejda Hodaj[15], Sylvain Jaffuel[16], Karine Lacombe[17], Fabrice Laine[18], Maeva Lefebvre[19], Zoha Maakaroun-Vermesse[20], Alain Makinson[21], Aurelie Portefaix[22], Valerie Pourcher[23,24], David Rey[25], David Zucman[26], Julie Longobardi[5], Mathilde Bertheau[27], Eric Tartour[28], Xavier de Lamballerie[29], Odile Launay[1,30,31,#], Linda Wittkop[5,32,33,#], For the ANRS0001s COV-POPART study group[$]

[1] *INSERM, F-CRIN, Reseau Innovative Clinical Research in Vaccinology (IREIVAC), Paris, France*
[2] *Service des Maladies Infectieuses et Tropicales, CHU de Nîmes, Nîmes, France*
[3] *INSERM U1047 – Université de Montpellier, Nîmes, France*
[4] *Vaccine Research Institute, INSERM et APHP, Hôpital H. Mondor, Créteil, France*
[5] *Univ. Bordeaux, INSERM, MART, Bordeaux, France*
[6] *Service d'infectiologie, CHU de Saint-Etienne, Saint-Étienne, France*
[7] *Service des Maladies Infectieuses et Tropicales, Hospices Civils de Lyon, Groupement Hospitalier Nord, Lyon, France, Lyon, France*
[8] *Université Claude Bernard Lyon 1, Centre International de Recherche en Infectiologie, Lyon, France*
[9] *Département de Médecine Infectiologique, Hôpital de L'archet, Centre Hospitalier Universitaire, Université Côte d'Azur, Nice, France*
[10] *Service des maladies infectieuses et tropicales, CHU d'Angers, Angers, France*
[11] *Centre d'Investigation Clinique 1415, AP-HM, Marseille, France*
[12] *INSERM CIC 1411, Centre Hospitalier Universitaire de Montpellier, Hôpital Saint-Eloi, Montpellier, France*
[13] *Service de Médecine Interne et Maladies Infectieuses, Hôpital Saint André, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France*
[14] *Univ. Bordeaux, INSERM, BPH, Bordeaux, France*
[15] *Inserm Centre d'Investigation Clinique 1406, Centre Hospitalier Grenoble-Alpes, Grenoble, France*
[16] *Service des Maladies Infectieuses et Tropicales, Brest, France*
[17] *Sorbonne Université, Inserm IPLESP, Service de maladies infectieuses et tropicales Hôpital Saint Antoine, Assistance Publique-Hôpitaux de Paris, Paris, France*
[18] *Université de Rennes, Centre Hospitalier Universitaire de Rennes, Rennes, France*
[19] *Service de maladies infectieuses et tropicales, Centre Hospitalier Universitaire Hôtel-Dieu, Nantes, France*
[20] *Centre Hospitalier Régional Universitaire Tours, Institut National de la Santé et de la Recherche Médicale CIC 1415, Tours, France*
[21] *Département des Maladies Infectieuses et Tropicales, Centre Hospitalier Universitaire de Montpellier & Université de Montpellier, Montpellier, France*
[22] *Hospices civils de Lyon, Centre Investigation Clinique, Bron, France*
[23] *Service de Maladies Infectieuses et tropicales, Hôpital de la Pitié Salpêtrière, Assistance Publique-Hôpitaux de Paris, Université de Paris Sorbonne, Paris, France*
[24] *Sorbonne Université, Inserm, Institut Pierre Louis d'Épidémiologie et de Santé Publique, Paris, France*
[25] *Le Trait d'Union, Centre de Soins de l'Infection par le VIH, NHC, Hôpitaux Universitaires, Strasbourg, France*
[26] *Réseau Ville-Hôpital, Service de Médecine Interne, Hôpital Foch, Suresnes, France*
[27] *ANRS Emerging Infectious Diseases, Paris, France*
[28] *Service d'Immunologie biologique, Hôpital européen Georges Pompidou/APHP, Paris, France*
[29] *Unité des Virus Emergents, Aix-Marseille Université, Institut de Recherche pour le Développement 190, Marseille, France*
[30] *Centre d'Investigation Clinique Cochin Pasteur, Paris, France*
[31] *Université de Paris, Paris, France*
[32] *INRIA SISTM Team, Talence, France*
[33] *CHU de Bordeaux, Service d'information médicale, INSERM, Bordeaux, France*

[*] Corresponding author: Paul Loubet, Service des Maladies infectieuses et Tropicales, CHU de Nîmes, Pr Robert Debré, 30029, Nîmes, France.
E-mail address: paul.loubet@chu-nimes.fr (P. Loubet).
[#] These authors contributed equally.
[$] The study group is listed in the Supplementary Materials.

https://doi.org/10.1016/j.ijid.2024.107110

ARTICLE INFO

Article history:
Received 8 March 2024
Revised 21 May 2024
Accepted 21 May 2024

Keywords:
SARS-CoV-2
Vaccines
HIV
Immunogenicity
COVID-19

ABSTRACT

Background: This study aimed to compare the humoral responses to mRNA COVID-19 vaccination in people living with HIV (PWH) and HIV-negative individuals.

Methods: We included PWH with an undetectable viral load under ART and HIV-negative participants from the French nationwide ANRS COV-POPART cohort who had received two doses of vaccine as a primary vaccination. We compared humoral response between controls and PWH, stratified by CD4 cell count ($<200/mm^3$ and $\geq 200/mm^3$ CD4 cell counts) at 1, 6, and 12 months after primary vaccination.

Results: A total of 1776 participants were included in this analysis, 684 PWH (99% were on ART, median CD4 counts 673 cells/mm^3) and 1092 controls. At 1 month, after adjustment on age, sex, and BMI, PWH had lower seroneutralization titers than controls, and PWH with <200 CD4 cell/mm^3 had lower anti-Spike SARS-CoV-2 IgG antibodies. Same results were found at 6 months. However, in participants who received a booster dose between 6 and 12 months postprimary vaccination, we did not observe differences between PWH and controls at 12 months.

Conclusion: PWH had high responses to primary mRNA COVID-19 vaccination. In those who received a booster dose after 6 months, the humoral response at 12 months increased to similar levels to controls, even in those with low CD4 counts at baseline.

Introduction

People living with HIV (PWH) are historically considered to have a lower and shorter response to vaccines compared to HIV-negative individuals [1,2]. These findings have led to recommendations for the use of vaccine regimens with higher antigen doses or adjuvants, exemplified by the recommendations for enhanced hepatitis B vaccination [3-6].

Besides known factors such as age and sex, markers of immunosuppression such as the nadir of CD4 T cell counts, CD4 T cell counts, and HIV viral load at vaccination, are the main predictive factors of vaccine response in PWH [7,8].

In the era of broad access to combined antiretroviral therapies (ART) and high compliance to ART in high-income countries, there is still uncertainty on differences in vaccine response between PWH and HIV-negative people. As an example, recent studies in PWH with CD4 cell counts above $350/mm^3$, and undetectable HIV-RNA showed similar 1 and 5-year immunogenicity following Yellow fever vaccination compared to healthy controls [9]. Recent meta-analyses showed that short-term immunogenicity following the COVID-19 vaccine primary series is slightly lower in PWH than controls, especially those with lower CD4 cell counts [8,10].

In France, the COVID-19 pandemic provided the opportunity to vaccinate a high portion of PWH, who were initially deemed to be at risk of severe forms of COVID-19, along with the general population. Both groups received the same vaccines and vaccination schedules, primarily consisting of mRNA COVID-19 vaccines.

We aimed to (i) compare the humoral response in PWH with suppressed HIV viral load with HIV-negative controls 1 and 6 months after mRNA COVID-19 primary two-dose vaccination, and at 12 months in those who received one mRNA vaccine booster dose, (ii) compare the neutralizing activity against variants of concern in a subset of PWH and HIV-negative controls.

Methods

Study design

ANRS0001S-COV-POPART (NCT04824651) is a multicenter prospective cohort study conducted in France, assessing the humoral immune response to COVID-19 vaccination in 11 specific populations and a control group. Participants from the ANRS0001S COV-POPART were included between March 25, 2021, and December 31, 2021, and followed for 24 months. The study design is further described in Supplementary Materials (Methods/Description of the ANRS0001S COV-POPART cohort) and previous publications [11,12].

In this study, we present the results of the cohort for up to 12 months.

Participants

In this study, we included PWH and HIV-negative control participants who received two doses of mRNA COVID-19 vaccines (BNT162b2 or mRNA-1273) 4 weeks apart as a primary vaccination, and whose antibody responses at 1 month after the second dose were available.

PWH with detectable HIV-RNA or other chronic conditions (e.g., diabetes mellitus, obesity, or immunosuppression [solid cancer, solid organ transplant]) known to impact the vaccine response [13] were excluded. The details on the chronic conditions are displayed in Supplementary Table 1.

Participants with COVID-19 infection defined as positive SARS-CoV-2 anti-nucleocapsid (NCP) antibodies or virologically confirmed COVID-19 before vaccination were excluded from the primary analyses. SARS-CoV-2 NCP antibodies were tested at each visit. Those with COVID-19 (virologically confirmed COVID-19 or positive NCP antibodies) during the follow-up were excluded from the subsequent analysis to describe vaccine-induced responses only. Complementary results, including these participants are presented in Supplementary Table 2.

Samples collection and laboratory assays

Serum samples were collected at inclusion and 1-, 6- and 12-months postsecond dose of COVID-19 vaccination. The samples analyzed as part of the study were managed and stored within the "Biobanque ANRS" before being sent for serological analyses to the "Unité des virus émergents" (Aix-Marseille Université, Institut de Recherche pour le Développement 190, Inserm 1207, Institut Hospitalo-Universitaire Méditerranée Infection—Marseille, France). Details on laboratory assays are available in Supplementary Materials (Methods/Laboratory Assay).

Outcomes

The main outcomes, compared between PWH and controls, were the raw percentage of responders (positive anti-Spike SARS-

CoV-2 IgG antibodies [ELISA], as defined by EuroImmun serology), geometric mean titers of anti-Spike SARS-CoV-2 IgG antibodies expressed in BAU/mL, and anti-SARS-CoV-2 specific neutralizing antibodies (nAbs) (*in vitro* neutralization assay for the original SARS-CoV-2 strain) at 1 month (21-56 days), at 6 months (+/−30 days) and at 12 months (+/−30 days) after the second dose of the primary vaccination regimen in those who received a vaccine booster dose after 6 months. Seroneutralization was performed only in participants with positive anti-Spike or anti-RBD SARS-CoV-2 IgG antibodies. For undetectable antibodies, half of the detection cut-off was imputed (i.e., 17.6 BAU/mL for anti-Spike SARS-CoV-2 IgG antibodies and a titer of 10 for seroneutralization antibodies).

Proportions of responders and geometric mean titers of anti-Spike SARS-CoV-2 IgG antibodies and anti-SARS-CoV-2-specific nAbs were estimated according to CD4 cells count ($<200/mm^3$ and $\geq 200/mm^3$ CD4 cell count) in PWH, at 1 and 6 months after primary vaccination and at 12 months after primary vaccination in those who received a booster after 6 months.

In vitro neutralization assays for the original SARS-CoV-2 strain and Delta and Omicron BA.1 variant were assessed in a subset of PWH and controls (the first 50 participants included in each group and having a positive serology [Spike or RBD] 1 month after the second dose).

Statistical analyses

The proportions of responders and their 95% confidence intervals (95% CI) were estimated using the Wilson score. The geometric mean of antibody titers and their 95% CI were estimated using a Student distribution. Humoral responses were compared between PWH and controls at 1, 6, and at 12 months only in those who received an mRNA booster dose after the 6-month visit using chi-square tests and Student's *t*-tests on log-transformed values of antibody titers.

Furthermore, we assessed the humoral response at 1 month following primary vaccination in PWH and controls using linear regression models. Separate models were used for anti-Spike and seroneutralization antibodies. The following variables were included in the models: a qualitative variable with 3 modalities (<200 CD4 cells/mm^3, ≥ 200 cells/mm^3, controls) an indicator variable allowing to compare controls with PWH with <200 CD4 cells/mm^3, and those with ≥ 200 cells/mm^3, sex (M/F), age (in years), BMI (underweight, normal, overweight) allowing for an adjusted comparison between PWH and controls. The response variables were log-transformed to respect underlying model assumptions. Model predictions were used to plot antibody titers by PWH CD4 groups and controls and by age for men and women separately in those with normal BMI. All statistical analyses were conducted with SAS (version 9.4).

Ethics

Written informed consent was obtained from each participant before enrollment, taking into account the GDPR (European Union General Data Protection Regulation) requirements. The protocol (N° EudraCT/ID-RCB: 2021-A00348-33) was conducted in accordance with the Declaration of Helsinki and the French law for research involving human subjects (known as Loi Jardé). The protocol was approved by Ethics Committees: the Committee for protection of persons engaged in Research "CPP Nord-Ouest IV" (file number: 21.02.12.47147) and the National Commission for Data Protection "CNIL" (Commission Nationale Informatique et Liberté, authorization number 921111v1).

Results

Characteristics of participants

Overall, 1776 participants were included in this analysis, 684 PWH, and 1092 controls (Figure 1). The median age was 51.2 years (interquartile range: 40.9-59.1) and 1061 (59.7%) were male. PWH were older than controls, more frequently males, and had more frequently CRP levels above the threshold limit (Table 1).

Among PWH, 99% were on ART (10 participants were "elite controllers"), and median CD4 count was 673 (496-856) cells/mm^3. Participants in both groups mainly received ($n = 1629$, 92%) two doses of BNT162b2 as the primary vaccination.

Raw humoral response at 1 month in PWH and controls

The percentage of anti-Spike SARS-CoV-2 IgG antibody responders at 1 month after the second dose of COVID-19 vaccine was lower in PWH than in controls (98.98% [97.9; 99.5] vs 99.91% [99.5; 99.9], $P = 0.0066$). Only seven PWH were nonresponders, 5 of whom had a CD4 cell count below 200/mm^3 (characteristics of the nonresponders are displayed in Supplementary Table 3).

Geometric means titers of anti-Spike SARS-CoV-2 IgG antibodies and anti-SARS-CoV-2-specific nAbs for the original SARS-CoV-2 strain were lower in PWH than in controls (1064.4, 95% CI [989.9-1144.6] vs 1500.3 95% CI [1435.8-1567.7], $P \leq 0.0001$ and 162.1 95% CI [147.8-177.9] vs 336.0 95% CI [315.7-357.7], $P \leq 0.0001$, respectively).

Among the 18 PWH with less than 200 CD4 cells/mm^3, 5 (27.8%) had negative anti-Spike SARS-CoV-2 IgG antibodies and 1 (7.7%) had positive anti-Spike antibodies but negative seroneutralization titers (vs 0.3% and 1.1% in those with $\geq 200/mm^3$).

Impact of baseline CD4 T cell count in humoral response to two doses of COVID-19 vaccines in PWH

After adjustment for age, sex, and BMI, anti-Spike SARS-CoV-2 IgG antibodies were similar to those of controls in PWH with CD4/mm^3 cell counts above 200. Conversely, PWH with a CD4/mm^3 cell count below 200 had a lower level of anti-Spike SARS-CoV-2 IgG antibodies than controls. While serum neutralization titers were higher in controls than in PWH, whatever the CD4 cell count at the time of vaccination, these titers were higher in PWH with a CD4 count >200 compared with those with a count <200 (Figure 2). Furthermore, anti-Spike SARS-CoV-2 IgG antibodies and seroneutralization titers against the original SARS-CoV-2 strain 1 month after the second dose were higher in women and decreased with age in both sexes, both in controls and in PWH. The estimated parameters of the linear regression models are displayed in Supplementary Tables 4 and 5.

Raw humoral response at 6 and 12 months in PWH and controls who received a booster dose after 6 months

At 6 months after the second dose of vaccine, before the booster dose, geometric mean titers of anti-Spike SARS-CoV-2 IgG antibodies and anti-SARS-CoV-2-specific nAbs for the original SARS-CoV-2 strain were lower in PWH than in controls (133.3 [123.2-144.1] vs 197.7 [186.2-209.9], $P \leq 0.0001$ and 43.7 [39.7-48.1] vs 64.9 [59.4-71.1], $P \leq 0.0001$, respectively) (Figure 3). Titers were slightly but non significantly lower in PWH with CD4 count $<200/mm^3$ compared to PWH with CD4 count $>200/mm^3$ (Figure 4).

Overall, 85% of PWH and 82% of controls received an mRNA booster dose after a median time of 6.2 months (6.0; 6.8) and 6.0

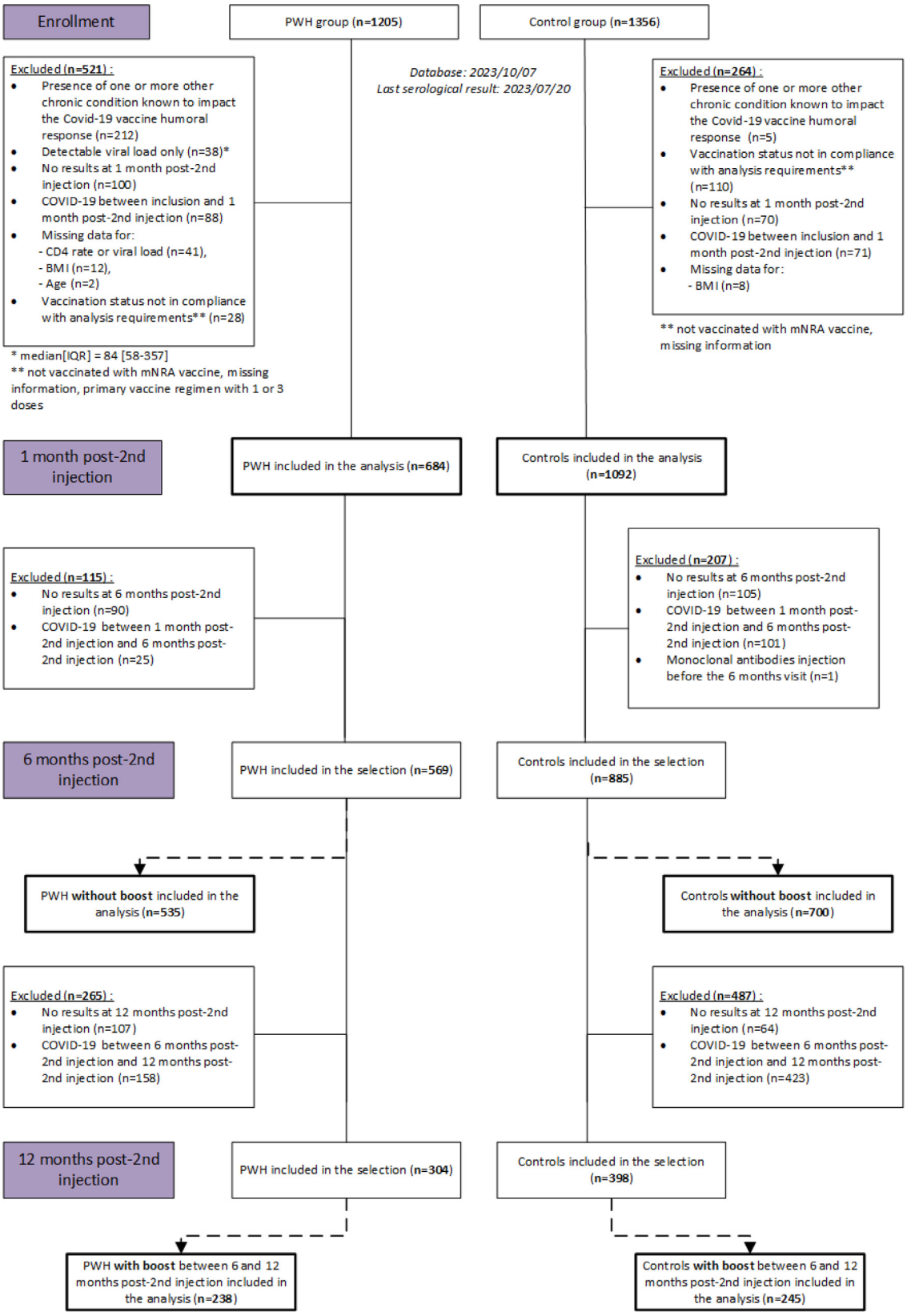

Figure 1. Flowchart of the participants included in the PWH sub-study of the ANRS COV-POPART cohort.

Table 1
Characteristics of PWH and controls included in the PWH sub-study of the ANRS COV-POPART cohort.

Characteristics median (IQR) or *n* (%)	PWH		Controls	
	N = 684		*N* = 1092	
Age (years)	55.4	(50.0-60.8)	46.3	(36.3-56.2)
Men	529	(77)	532	(49)
Body mass index	23.8	(21.8-25.8)	23.4	(21.4-25.9)
CDC stage				
A	424	(62)	-	-
B	112	(16)	-	-
C	137	(20)	-	-
NA	11	(2)	-	-
Antiretroviral therapy	674	(99)	-	-
CD4 count at inclusion (cells/mm^3)	673	(496-856)	-	-
CD4 count <200 cells/mm^3	18	(3)	-	-
C Reactive Protein at inclusion >5 mg/L	62	(9)	49	(5)
Primary vaccination regimen (2 doses)				
BNT162b2 + BNT162b2	645	(94)	984	(90)
mRNA-1273 + mRNA-1273	37	(5)	100	(9)
BNT162b2 + mRNA-1273	1		4	(0.5)
mRNA-1273 + BNT162b2	1		4	(0.5)
Number of days between the two doses of the primary vaccination regimen	28	(28-38.5)	39	(28-42)
Number of participants who received a booster dose	580	(85)	897	(82)
Booster type				
BNT162b2	490	(85)	551	(62)
mRNA-1273	77	(13)	317	(35)
Not available	13	(2)	29	(3)
Number of months between second dose and booster	6.2	(6.0-6.8)	6.0	(5.6-6.2)
Number of months between booster and sample collection at 12 months	6.3	(6.0-6.7)	6.5	(6.1-6.9)

PWH, people living with HIV.

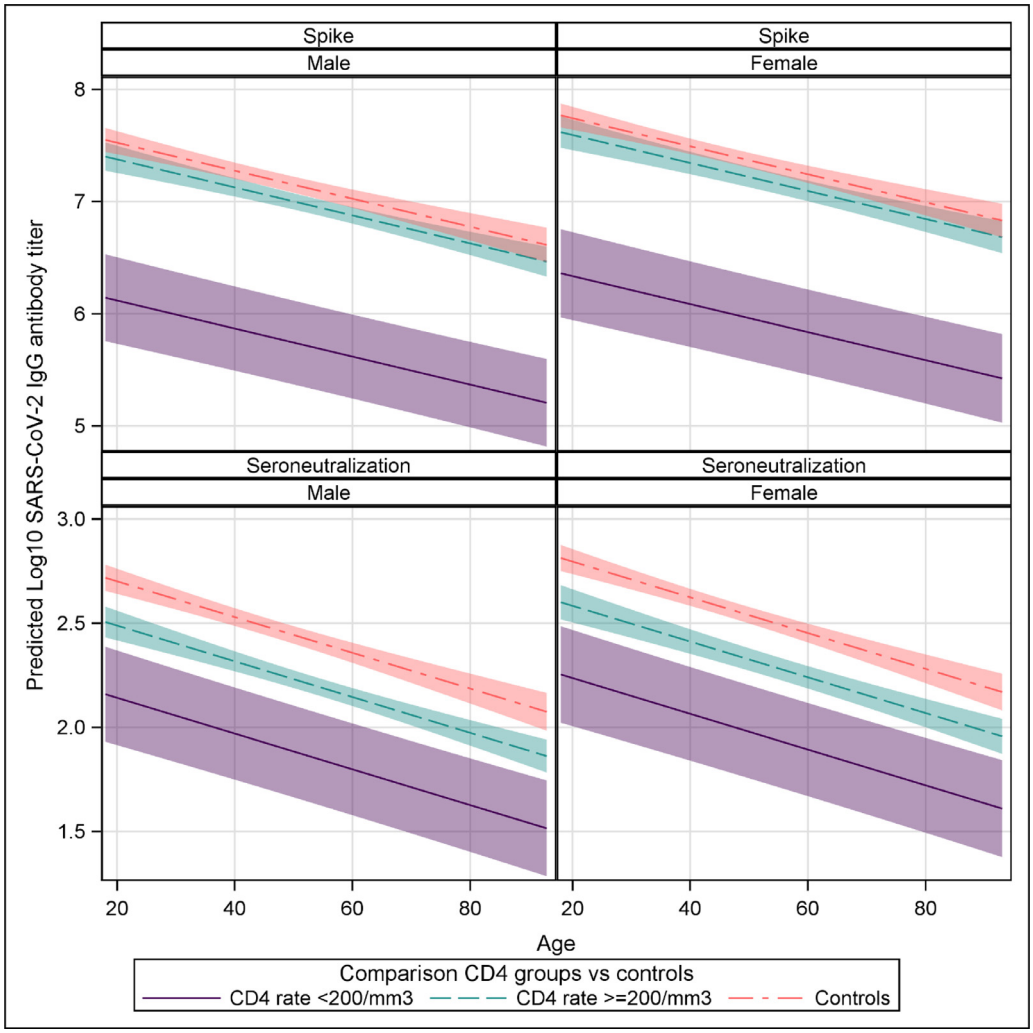

Figure 2. Prediction trends with 95% CI of linear regression analysis for age and sex of anti-Spike SARS-CoV-2 IgG antibody titers and seroneutralization (against original strain) at 1 month following mNRA COVID-19 primary vaccination in PWH and controls with normal BMI in the PWH sub-study of the ANRS COV-POPART cohort.

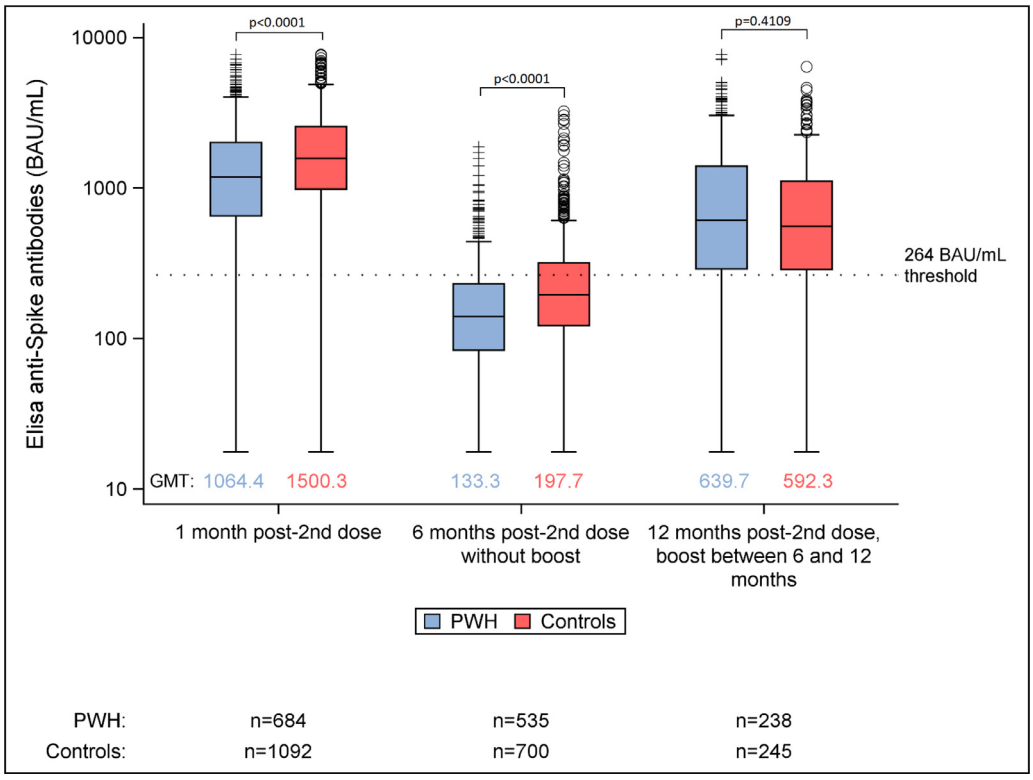

Figure 3. Median (IQR) and geometric mean (GMT) of anti-Spike SARS-CoV-2 IgG antibody titers at 1, 6, and 12 months following mRNA COVID-19 primary vaccination in PWH and controls in the PWH sub-study of the ANRS COV-POPART cohort.

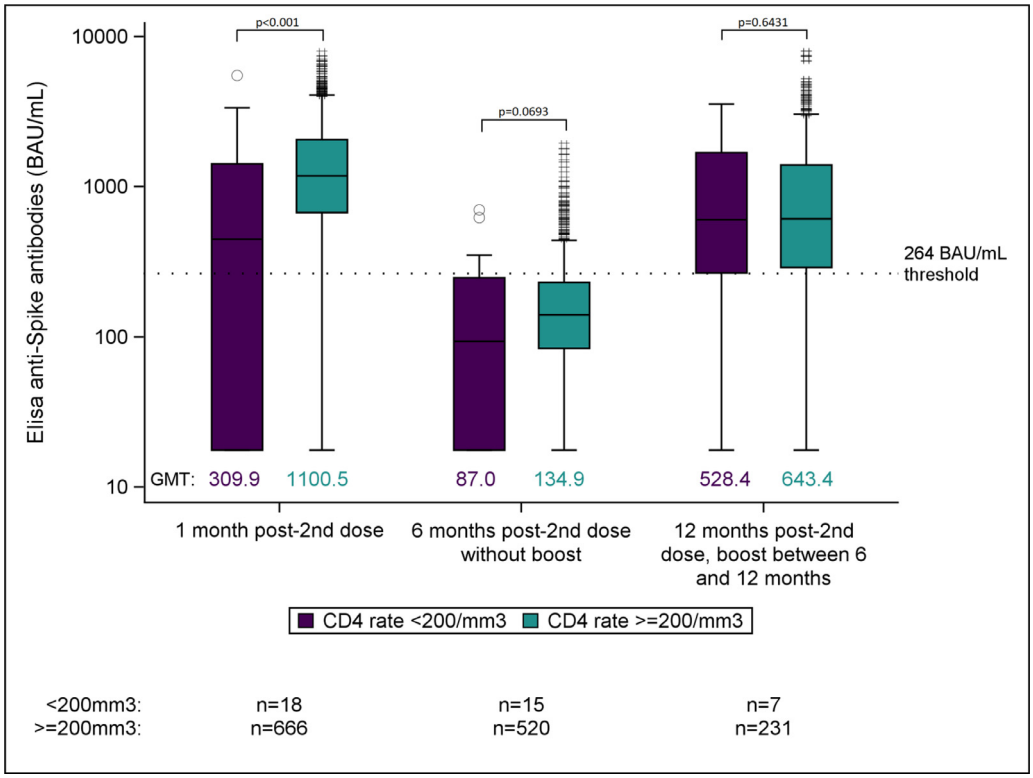

Figure 4. Median (IQR) and geometric mean (GMT) of anti-Spike SARS-CoV-2 IgG antibody titers at 1, 6, and 12 months following mRNA COVID-19 primary vaccination in PWH and controls according to CD4 count level at inclusion in the PWH sub-study of the ANRS COV-POPART cohort.

months (5.6; 6.2) after the second dose, respectively. Characteristics of PWH and controls according to the receipt of a booster dose are displayed in Supplementary Tables 6 and 7.

In those who received the booster dose, the levels of anti-Spike SARS-CoV-2 IgG antibodies at 12-month after the second dose were similar between PWH and controls (639.7 [555.5; 736.6] vs 592.3 [526.2; 666.8] $P = 0.4109$) (Figure 3), whereas nAbs for the original SARS-CoV-2 strain were significantly higher in PWH (384.4 [309.8; 477.0] vs 273.9 [226.6; 331.1] $P = 0.0203$). There was no difference according to the baseline CD4 count level (Figure 4).

We found similar results when including participants with positive SARS-CoV-2 anti-NCP antibodies between inclusion and 12-month visit, with higher levels of anti-Spike antibodies and neutralization titers overall than in participants with negative anti-NCP antibodies (Supplementary Table 2).

Neutralization of VariantsVariants of concern

Compared to controls, PWH had significantly lower nAbs against original and Delta strains and nonsignificantly lower nAbs titers against Omicron BA.1 strain at 1 month (123.7 vs 188.7, $P = 0.0448$; 57.7 vs 99.0, $P = 0.0213$ and 12.4 vs 13.9, $P = 0.3588$) and 6 months after the second vaccine dose (35.0 vs 58.6, $P = 0.0367$; 18.3 vs 25.5, $P = 0.0682$ and 11.2 vs 10.5, $P = 0.3525$).

The booster dose received after 6 months significantly increased the titers of nAbs against original and Delta strains and, to a lower extent, against Omicron in both groups at 12 months (Supplementary Figure 1).

Discussion

The COVID-19 pandemic allowed, for the first time, the assessment of the immunological and clinical responses to a new vaccine platform, mRNA vaccines, in various populations, naïve to previous antigenic stimulation (infection or vaccination) at the time of primary vaccination.

To our knowledge, this is the largest study to date comparing humoral response to COVID-19 mRNA vaccines after both primary and booster vaccination in PWH and controls with standardized and centralized assessment of antibody responses.

Our population was representative of PWH in high-income countries, primarily males with a median age of around 55 years and high rates of viral load control under c-ART. However, in order to have a homogeneous population, we chose to exclude PWH participants with uncontrolled HIV viral load (who represented less than 5% of the PWH participants in the study, and because vaccination should be postponed until control of the viral load in these patients) or harboring other conditions known to negatively impact the humoral response. Participants with confirmed COVID-19 before inclusion or during the follow-up (based on virologically confirmed declared COVID-19 or positive anti-NCP) were excluded from the different analyses in order to assess the humoral response to the vaccine only.

We showed that the percentage of responders to two doses of mRNA COVID-19 vaccines as a primary vaccination in PWH participants was very high (despite a significant but not biologically meaningful small difference). In contrast, the quantitative response was significantly lower for anti-Spike SARS-CoV-2 IgG antibodies and anti-SARS-CoV-2-specific nAbs for the original SARS-CoV-2 strain compared to controls.

The model adjusted for age, sex, BMI, and CD4 count confirmed that PWH had lower levels of neutralization titers than controls, especially in those with CD4 counts below 200/mm^3. This implies the assessment of intensified vaccination protocols to improve the humoral response of people with low CD4 counts who need vaccination without waiting for CD4 restoration.

Advanced age and male sex predicted lower neutralization response in both PWH and controls, per the literature in both COVID-19 [14] and other existing vaccines [15,16].

Our results confirm results from a recent meta-analysis showing that PWH demonstrates reduced seroconversion and neutralization responses after primary vaccination when compared with controls and appear to experience more breakthrough infections, especially in the context of lower CD4$^+$ T-cell counts [8,17,18].

Interestingly, receiving a booster dose on average 6 months after the end of the primary vaccination regimen increased both anti-Spike SARS-CoV-2 IgG antibodies and anti-SARS-CoV-2-specific nAbs at 12 months to similar or significantly higher levels compared to controls, even in those with CD4 counts below 200/mm^3 at inclusion. Of note, only 7 PWH with CD4 counts <200 were included in the comparison at month 12.

Our results are in line with other studies on the benefit of a booster dose on immunogenicity in PWH [19-21] including those with low CD4 count [22]. However, these studies had a limited postbooster follow-up (4-8 weeks) except for the study by Heftdal et al., [23] which had a follow-up until 11 months after the first booster (third dose) and showed similar antibody concentrations and cellular response between PWH and controls. Our data on a large sample of PWH compared to a control group with centralized and standardized analyses and measurements of nAbs add information on the extended benefit (up to 6 months) of this booster dose.

This underlines the fact that PWH generally benefits from booster doses and is in line with what has been showed with the sub-optimal immunological response to standard HBV vaccination and the waning of hepatitis B immunity in PWH [24].

Without a clearly defined correlate of protection, it is impossible to assess whether these biological differences are clinically relevant.

The main limitations of the work are the lack of data on cellular response and clinical efficacy. This will be addressed in the future, as data collected from participants in the COV-POPART study will be linked to the French nationwide healthcare data system (https://www.health-data-hub.fr/), so that the humoral response of PWH participants will be correlated to clinical efficacy on COVID-19 related deaths and hospitalizations. Strengths of this multicentric study include its large sample of PWH, the use of a control group, the standardized timeline of assessment, and the standardized centralized analyses of the results.

In conclusion, these results show that PWH receiving ART and with an undetectable viral load have a good response rate but an overall lower quantitative humoral response 1 month after receiving two doses of COVID-19 mRNA vaccines than controls. CD4 count below 200/mm^3, age, and male sex negatively impacted this response. A first booster dose 6 months after the primary vaccination durably increased this response to levels similar to those observed in controls at 12 months.

Funding

The ANRS0001S COV-POPART cohort is conducted with the support of Inserm—ANRS MIE and funded by French ministries: Ministère des Solidarités et de la Santé and Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation

Author Contributions

PL and LW drafted the first version of the manuscript; PL and LW designed the study and interpreted the data. LW and AF did all analyses and are guarantees for the analyses. Data was acquired by PL, OL, JDL, AM, AP, BD, CC, DC, DR, DZ, EB, EH, FG, FL, KL, MH, ML, SJ, VD, VP, ZM and the COV-POPART study group. OL, LW, JDL, AF,

XDL, ET, JL, MB, AM, AP, BD, CC, DC, DR, DZ, EB, EH, FG, FL, KL, MH, ML, SJ, VD, VP, ZM, critically revised the manuscript. All members of the COV-POPART writing group and study group were involved in the review of the final manuscript.

Declarations of competing interest

PL has received payment or honoraria for lectures, presentations, speakers bureau, manuscript writing, or educational events from AstraZeneca, GlaxoSmithKline, Janssen, Moderna, Merck Sharp & Dohme, Pfizer, Sanofi Pasteur, Seqirus. KL has received payment or honoraria for lectures, presentations or educational events from GlaxoSmithKline, Moderna, Merck Sharp & Dohme, Gilead. ZM has received payment or honoraria for lectures and presentations from Sanofi Pasteur, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer. VP has received honoraria for lectures and presentations from Moderna. OL has received payment or honoraria for lectures, presentations, speakers bureau, or educational events from Sanofi Pasteur; Pfizer, Janssen, Moderna, Merck Sharp & Dohme, Seqirus and grants from Sanofi Pasteur; Pfizer, Janssen, GlaxoSmithKline, Moderna. The other authors declare having no conflict of interest.

Acknowledgments

The authors would like to thank all participants, the dedicated staff of the local centers and their respective biological resource centers, who continuously participate with enthusiasm in the cohort and make this research possible. Without their commitment, a cohort of this magnitude would not be possible. We thank the UMS 54 MART (Methods and Applied Research for Trials) Univ. Bordeaux, INSERM for the methodology, statistical analysis, data management, data monitoring, and ANRS0001S COV-POPART cohort management. We thank as well the ANRS SC10 US019 INSERM Biobank for its huge ongoing contribution in this project, the Steering Committee, the Scientific Steering Committee, the Emerging Viral Diseases (UVE), the Biological Immunology Service (HEGP APHP), the ANRS0001S COV-POPART Study Group and the F-CRIN I-Reivac Network team for their support. This study is sponsored by Inserm-ANRS MIE and has been labeled as a National Research Priority by the National Orientation Committee for Therapeutic Trials and other researcher on COVID-19 (CAPNET). The investigators would like to acknowledge ANRS Emerging Infectious Diseases for their scientific support, the French Ministry of Health and Prevention, and the French Ministry of Higher Education, Research and Innovation for their funding and support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107110.

References

[1] Beck CR, McKenzie BC, Hashim AB, Harris RC, Nguyen-Van-Tam JS. Influenza vaccination for immunocompromised patients: systematic review and meta–analysis by etiology. *J Infect Dis* 2012;**206**(8):1250–9.
[2] Kernéis S, Launay O, Turbelin C, Batteux F, Hanslik T, Boëlle PY. Long-term immune responses to vaccination in HIV-infected patients: a systematic review and meta-analysis. *Clin Infect Dis* 2014;**58**(8):1130–9.
[3] Zhang W, Sun H, Atiquzzaman M, Sou J, Anis AH, Cooper C. Influenza vaccination for HIV-positive people: systematic review and network meta-analysis. *Vaccine* 2018;**36**(28):4077–86.
[4] Launay O, van der Vliet D, Rosenberg AR, Michel ML, Piroth L, Rey D, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. *JAMA* 2011;**305**(14):1432–40.
[5] Launay O, Desaint C, Durier C, Loulergue P, Duval X, Jacomet C, et al. Safety and immunogenicity of a monovalent 2009 influenza A/H1N1v vaccine adjuvanted with AS03A or unadjuvanted in HIV-infected adults: a randomized, controlled trial. *J Infect Dis* 2011;**204**(1):124–34.
[6] Vargas JI, Jensen D, Martínez F, Sarmiento V, Peirano F, Acuña P, et al. Comparative efficacy of a high-dose vs standard-dose hepatitis B revaccination schedule among patients with HIV. *JAMA Netw Open* 2021;**4**(8):e2120929.
[7] Catherine FX, Piroth L. Hepatitis B virus vaccination in HIV-infected people: a review. *Hum Vaccin Immunother* 2017;**13**(6):1304–13.
[8] Griffin DWJ, Pai Mangalore R, Hoy JF, McMahon JH. Immunogenicity, effectiveness, and safety of SARS-CoV-2 vaccination in people with HIV. *AIDS* 2023;**37**(9):1345–60.
[9] Colin de Verdiere N, Durier C, Samri A, Meiffredy V, Launay O, Matheron S, et al. Immunogenicity and safety of yellow fever vaccine in HIV-1-infected patients. *AIDS* 2018;**32**(16):2291–9.
[10] Zhao T, Yang Z, Wu Y, Yang J. Immunogenicity and safety of COVID-19 vaccines among people living with HIV: a systematic review and meta-analysis. *Epidemiol Infect* 2023;**151**:e176.
[11] Loubet P, Wittkop L, Tartour E, Parfait B, Barrou B, Blay JY, et al. A French cohort for assessing COVID-19 vaccine responses in specific populations. *Nat Med* 2021;**27**:1319–21.
[12] Loubet P, Wittkop L, Ninove L, Chalouni M, Barrou B, Blay JY, et al. One-month humoral response following two or three doses of messenger RNA coronavirus disease 2019 vaccines as primary vaccination in specific populations in France: first results from the Agence Nationale Recherche contre le Sida (ANRS)0001S COV-POPART cohort. *Clin Microbiol Infect* 2023;**29**(3):388.e1–388.e8.
[13] Gaborit B, Fernandes S, Loubet P, Ninove L, Dutour A, Cariou B, et al. Early humoral response to COVID-19 vaccination in patients living with obesity and diabetes in France. The COVPOP OBEDIAB study with results from the ANRS0001S COV-POPART cohort. *Metabolism* 2023;**142**:155412.
[14] Collier DA, Ferreira IATM, Kotagiri P, Datir RP, Lim EY, Touizer E, et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. *Nature* 2021;**596**(7872):417–22.
[15] Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D. Vaccination in the elderly: the challenge of immune changes with aging. *Semin. Immunol* 2018;**40**:83–94.
[16] Harper A, Flanagan KL. Effect of sex on vaccination outcomes: important but frequently overlooked. *Curr Opin Pharmacol* 2018;**41**:122–7.
[17] Galmiche S, Luong Nguyen LB, Tartour E, de Lamballerie X, Wittkop L, Loubet P, et al. Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review. *Clin Microbiol Infect* 2022;**28**:163–77.
[18] Lee ARYB, Wong SY, Chai LYA, Lee SC, Lee MX, Muthiah MD, et al. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. *BMJ* 2022;**376**:e068632.
[19] Gianserra L, Donà MG, Giuliani E, Stingone C, Pontone M, Buonomini AR, et al. Immunogenicity and safety of BNT162b2 homologous booster vaccination in people living with HIV under effective cART. *Vaccines (Basel)* 2022;**10**(8):1243.
[20] Corma-Gómez A, Fernández-Fuertes M, Viñuela L, Domínguez C, Santos M, Fuentes-López A, et al. Reduced neutralizing antibody response to SARS-CoV-2 vaccine booster dose in people living with HIV with severe immunosuppression. *J Med Virol* 2023;**95**(3):e28602.
[21] Jongkees MJ, Geers D, Hensley KS, Huisman W, GeurtsvanKessel CH, Bogers S, et al. Immunogenicity of an additional mRNA-1273 SARS-CoV-2 vaccination in people with HIV with hyporesponse after primary vaccination. *J Infect Dis* 2023;**227**(5):651–62.
[22] Vergori A, Cozzi Lepri A, Cicalini S, Matusali G, Bordoni V, Lanini S, et al. Immunogenicity to COVID-19 mRNA vaccine third dose in people living with HIV. *Nat Commun* 2022;**13**:4922.
[23] Heftdal LD, Pérez-Alós L, Hasselbalch RB, Hansen CB, Hamm SR, Møller DL, et al. Humoral and cellular immune responses eleven months after the third dose of BNT162b2 an mRNA-based COVID-19 vaccine in people with HIV – a prospective observational cohort study. *EBioMedicine* 2023;**93**:104661.
[24] Farooq PD, Sherman KE. Hepatitis B vaccination and waning hepatitis B immunity in persons living with HIV. *Curr HIV/AIDS Rep* 2019;**16**(5):395–403.