Efficacia e sicurezza del vaccino a mRNA anti SARS-CoV-2 nelle persone che vivono con HIV.

Efficacy and safety of mRNA vaccine anti SARS-CoV-2 in people living with HIV.

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Riassunto

In letteratura sono disponibili pochi studi sull'efficacia e la sicurezza dei vaccini a mRNA nelle persone che vivono con l'infezione da HIV (PWH). Con lo scopo di valutare lo sviluppo di anticorpi per SARS-CoV-2 nelle PWH, dopo la vaccinazione, abbiamo svolto uno studio prospettico, arruolando le PWH che sono state vaccinate tra marzo e luglio 2021. Tutti sono stati vaccnati con BNT162b2 (Cominarty®), due dosi a distanza di 21 giorni. Abbiamo valutato la presenza di anticorpi per SARS-CoV-2 prima della prima dose (T0 e T1) e 12 settimane dopo la seconda dose (T2). Il dosaggio degli anticorpi è stat effettuato con LIAISON® SARS-CoV-2 TrimericS IgG di DiaSorin. In aggiunta, le cellule ematiche sono state esaminate a T0, T1 e T2.

Abbiamo incluso 185 PWH, di età mediana 54 anni (interquartile range 46-58; di questi, 52 (28.1%) erano donne. Per quanto riguarda i fattori di rischio, 62 (33.5%) erano stati utilizzatori di droghe endovenose (PWID). Al basale, 21 (11.3%) PWH risultavano aver già avuto un'infezione da SARS-CoV-2, 17 (9.2%) avevano HIV RNA rilevabile. Solo 7 (3.8%) avevano una conta dei CD4 <200 CD4 cells/mm^3.

175 (94.6%) PWH hanno sviluppato IgG dopo la prima dose, e 184 (99.5%) dopo la seconda. Lo sviluppo di IgG era più alto nelle persone con precedente infezione da SARS-CoV-2, mentre era più basso nelle PWID, nei fumatori, nelle persone con basso nadir dei CD4, e in chi aveva HIV RNA rilevabile. 127 (68.6%) e 146 (78.9%) PWH hanno riportato eventi avversi dopo la prima e la seconda dose, rispettivamente, con una prevalenza più alta tra chi aveva avuto una precedente infezione da SARS-CoV-2 (95% vs 76.8%, p<0.001).

Abstract

Few studies regarding the efficacy and safety of mRNA vaccines in people living with HIV (PWH) are available in the literature. We aimed to evaluate the development of SARS-CoV-2 antibodies in PWH after vaccination.

We conducted a prospective study enrolling PWH who received SARS-CoV-2 vaccination between March and July 2021. All people have been vaccinated with BNT162b2 (Cominarty®) with two doses separated by 21 days. We evaluated the presence of SARS-CoV-2 antibodies before the doses (T0 and T1) and 12 weeks after the last dose (T2). In particular, antibodies were evaluated with LIAISON® SARS-CoV-2 TrimericS IgG by DiaSorin. In addition, a blood cell examination was performed at T0, T1 and T2.

We included 185 PWH; of these 52 (28.1%) were female, with a median age of 54 (IQR 46-58) years. Regarding HIV risk factors, 62 (33.5%) were previous injection drug users (PWID). At baseline, 21 (11.3%) PWH had been previously infected by SARS-CoV-2, 17 (9.2%) had a detectab le HIV-RNA; only 7 (3.8%) had <200 CD4 cells/mm^3. 175 (94.6%) PWH developed IgG after the 1st dose and 184 (99.5%) after the 2nd dose. IgG development was higher in people previously infected by SARS-CoV-2 and lower in PWID, smokers, low CD4 nadir, and detectable HIV-RNA. 127 (68.6%) and 146 (78.9%) PWH reported adverse events after the 1st and 2nd dose, respectively, with a higher prevalence in PWH with previous SARS-CoV-2 infection (95% vs 76.8%, p<0.001).

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A tre mesi dalla seconda dose del vaccino anti-SARS-CoV-2, 99.5% delle PWH avevano IgG rilevabili, suggerendo che le due dosi di vaccino, somministrate a distanza di 21 giorni sono critiche per ottenere tassi ottimali di seroconversione nelle PWH.

After three months since the second dose of the anti-SARS-CoV-2 vaccine, 99.5% of PWH had detectable IgG, suggesting that 21 days apart two doses of mRNA vaccine are critical for PWH to achieve optimal seroconversion rates.

Background

Globally, more than 650 million of infections have been infected with SARS-CoV-2, the causative virus of CoronaVIrus Disease (COVID-19). COVID-19 could be asymptomatic or paucisymptomatic in the majority of infected individuals (1). In the symptomatic forms, the most prevalent symptoms are a fever, a cough, and dyspnea. At the same time, a low proportion of patients complain of gastrointestinal symptoms, anosmia, dysgeusia, headaches, and skin lesions (2–7). In a minority of cases, the infection can be associated with life-threatening systemic inflammation, respiratory failure, and multiorgan dysfunction (8–10).

Many studies have been conducted to individualize which people could have a higher risk of disease progression. In the majority of studies, the principal conditions related to disease progression and death were advanced age, obesity, chronic obstructive pulmonary disease, and immunodeficiency, including HIV. Geretti et al. showed how PWH had an increased risk of dying compared with people without HIV (PWoH), especially if the CD4 count was < 200 cells/mm^3. However, a meta-analysis showed how PWH on antiretroviral treatment and with a CD4 count > 350 cells/mm^3 had the same risk of PWoH. On the contrary, those with a detectable viral load and a low CD4 cell count had an increased risk of death (11–13).

For these reasons, PWH have been included in those categories of diseases which have priority for vaccination. In addition, many studies have been conducted on vaccination's safety, immunogenicity, and efficacy on PWH, with heterogeneous results (14,15). Therefore, our study aimed to evaluate the development of SARS-CoV-2 antibodies in PWH after vaccination.

Methods

We conducted a prospective study enrolling PWH who received SARS-CoV-2 vaccination between March and July 2021.

All people have been vaccinated with BNT162b2 (Cominarty®) with two doses separated by 21 days.

We evaluated the presence of SARS-CoV-2 antibodies before the doses (T0 and T1) and 12 weeks after the last dose (T2). In particular, antibodies were evaluated with LIAISON® SARS-CoV-2 TrimericS IgG by DiaSorin. In addition, a blood cell examination was performed at T0, T1 and T2.

We collected demographical data, medical history (HCV and HBV-coinfection, comorbidities, CD4 nadir, HIV-RNA zenith, CDC stage, history of intravenous drug use, history of opportunistic infections, previous SARS-CoV-2 infection), last CD4 and CD8 cell count, and last HIV-RNA.

We excluded from the study people who performed only one vaccine dose and those who refused to sign the written informed consent. In this case, the patients received the vaccination but were not included in the study.

Statistical analysis

Quantitative variables were summarised with medians and 25th–75th percentiles (interquartile range, IQR), whereas qualitative ones with absolute and relative (percentages) frequencies. The Shapiro–Wilk test was used to assess the normality of quantitative data. The Mann–Whitney test evaluated subgroup differences for quantitative variables. Finally, Spearman's rank correlation coefficient was used to assess differences for quantitative variables. A two-tailed p-value less than 0.05 was considered statistically significant. All statistical analyses were performed with STATA version 17 (StatsCorp, TX, USA).

Results

Between March and July 2021, 205 PWH were vaccinated in our outpatient clinic. Five of these were excluded from the study because they refused to sign the written informed consent, and 15 were excluded because they only received the first dose vaccine.

For these reasons, we included in the study 185 PWH; of these 52 (28.1%) were female.
The median age was 54 (IQR 46-58) years.

Variable	N (%) or median (IQR)
Age years, median (IQR)	54 (46-58.0)
Female, n (%)	52 (28.1)
Male, n (%)	138 (71.9)
Way of transmission, n (%)	
- Heterosexual	57 (30.8)
- MSM	62 (33.5)
- IDU	62 (33.5)
- Vertical	2 (1.1)
- Sex workers	2 (1.1)
Smoking, n (%)	
- Former	97 (52.4)
- Ex	23 (12.4)
- Never	65 (35.2)
Alcool, n (%)	
- Yes	24 (13.0)
- No	161 (87.0)
Coinfection, n (%)	
- HCV	57 (30.8)
- HBV	29 (15.7)
Comorbidity, n (%)	
- Diabetes	8 (4.3)
- COPD	14 (7.6)
- Kidney Failure	5 (2.7)
- Hypertension	41 (22.2)
- CHD	13 (7.0)
- Cancer	17 (9.2)
- Obesity	19 (10.3)
HIV duration, years, median (IQR)	16 (10-27)
Zenith HIV-RNA, copies/mL, median (IQR)	120'000 (47'000-190'000)
Nadir CD4, cell/mm^3, median (IQR)	301 (156-477)
CD4 nadir <200 cells/mm^3, n (%)	56 (30.3)
CDC stage C, n (%)	46 (24.9)
Current CD4 cell count, cell/mm^3, median (IQR)	777 (572-987)
Current CD8 cell count, cell/mm^3, median (IQR)	869 (646-1214)
Previous SARS-CoV-2 infection, n (%)	21 (11.4)

IQR: Interquartile Range;
MSM: man who had sex with man;
IDU: injection drug user;
COPD: Chronic obstructive pulmonary disease;
CHD: cardiovascular disease.

Table 1. Characteristics of 192 people living with HIV who received SARS-CoV-2 mRNA vaccine.

Regarding HIV risk factors, 62 (33.5%) were previous injection drug users (PWID), and 62 (33.5) were men who had sex with men (MSM).
Regarding the HIV history data, the median of the infection's duration was 16 (10-27) years, with the median of CD4 nadir being 301 (156-477) cells/mm^3; 56 (30.3%) people who had a nadir lower than 200 cells/mm^3.
In addition, 46 (24.9%) people have had at least one opportunistic infection **(Table 1)**.
At the first vaccination (T0), the current CD4 cells median count was 777 (IQR 572-987) cells/mm^3. Seventeen (9.2%) people had a detectable HIV-RNA, and only 7 (3.8%) had <200 CD4 cells/mm^3. Seven people referred that they had had SARS-COV-2 infection; however, 17 (9.2%) had positive IgG anti-SARS-CoV-2 at T0, consistent with previous asymptomatic infection. On the contrary, four people who referred a previous SARS-CoV-2 infection did not have detectable IgG anti-SARS-CoV-2.
One hundred seventy-five (94.6%) PWH developed IgG after the 1st dose (T1) and 184 (99.5%) after the 2nd dose (T2). IgG development was higher in people previously infected by SARS-CoV-2 and lower in PWID, smokers, low CD4 nadir, and detectable HIV-RNA **(Table 2)**.
In the multivariate analysis, also IDU resulted in having lower IgG anti-SARS-CoV-2 levels **(Table 3)**.
Finally, we investigate the adverse effect on this population.
Overall, 127 (68.6%) and 146 (78.9%). PWH reported adverse events after the 1st and 2nd dose, respectively, with a higher prevalence in PWH with previous SARS-CoV-2 infection (95% vs 76.8%, p<0.001).

Variable	Yes	No	P
HCV	345 (167-580)	560 (254-925)	0.0092
Female Gender	562 (269-1050)	479 (199-803)	0.17
Current smoker	361 (153-640)	731 (349-1190)	<0.00001
Previous SARS-CoV-2 infection	1900 (1230-4610)	439(201-764)	<0.00001
IDU	486(232-866)	496 (212-838)	0.79
NADIR <200 CD4 cells/mL	357 (176-806)	526 (266-866)	0.0683
HIV-RNA > 50 cp/mL	226 (95-278)	513 (242 – 888)	0.0015

Table 2. Median (IQR) of IgG anti-SARS-CoV-2 according to different variables.

Variables	Rho	95% CI for Rho	p-value*
IDU	-0.152	-0.287 – -0.011	0.035
Kidney Failure	0.009	-0.133 – 0.15	0.901
AIDS presentation	-0.118	-0.255 – 0.0233	0.101
Smoking	-0.238	-0.367 – -0.100	0.001
Nadir CD4 cell/mm^3	0.201	0.062 – 0.333	0.005
CD4 Nadir <200 cell/mm^3	-0.189	-0.321– -0.049	0.009
HBV coinfection	-0.011	-0.152 – 0.13	0.877
Current HIV-RNA	-0.166	-0.300 – -0.025	0.021

Table 3. Correlation (Spearman's rank correlation coefficient) between clinical and viroimmunological characteristics and IgG anti-SARS-CoV-2 levels.

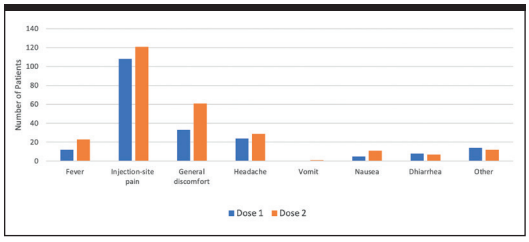

Figure 1. Number of patients who complained about adverse effects after the vaccination with BNT162b2.

However, no serious adverse events were reported **(Figure 1).**

Discussion

In our study, we found that two doses of mRNA vaccine against SARS-CoV-2 guaranteed a good IgG production almost in all PWH, confirming the efficacy of the mRNA vaccine in this specific population.

It is important to note that no mRNA vaccine trials have been conducted in PWH.

The only trial available is about AZD1222/ChAdOx1 vaccine (Astrazeneca), in which 54 PWH were compared to 50 people without HIV (PWoH) after receiving two vaccine doses. They have not found a correlation between the magnitude of anti-spike IgG and CD4 cell count, and there is no difference between the two cohorts (16). On the contrary, real-life studies on mRNA vaccines showed that PWH had a lower level of IgG than PWoH (14,15). Several other studies confirmed this results (17,18). In addition, Schmidt et al. found a significantly lower level of SARS-CoV-2-specific IgA in PWH than in PWoH, indicating a moderately lower functionality of the humoral vaccine response (14,18).

Other studies found a significant difference in neutralizing antibody responses between PWH with a CD4:CD8 ratio < 0.5 or less than 200/250 CD4 cells/mm^3 (19–23).

On the contrary, Portillo et al. found no evidence of poorer viral neutralization in PWH compared to PWoH (24). Comparing our study with the previous studies conducted before is difficult due to the differences in vaccine used and different methodologies for individuating the IgG level.

However, similar to them we found a correlation between the lower CD4 cell count and a lower response rate. Regarding safety, the majority of the studies present in the literature have not reported notable adverse events. In the previous trial, the most common were pain at the injection site (49), fatigue (47%), headache (47%), and malaise (34%). We had higher complaints about injection site pain (58.4% after first dose, 65.4% after the second dose), while the percentage of people with headache and malaise was lower. In addition, we compared the adverse effects percentage after the first and second doses, with an increased number of adverse events.

However, we have also not registered any serious adverse effects in our study. In conclusion, we observed that after three months since the second dose of the anti-SARS-CoV-2 vaccine, 99.5% of PWH had detectable IgG. However, lower IgG has been registered in people with IDU history, smokers, people with a low CD4 nadir cell count and with a detectable HIV-RNA. Therefore, further studies should be performed to understand the necessity of further booster doses in PWH with a good immunologic status. ■

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