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Humoral response to anti-COVID-19 immunization and SARS-CoV-2 infection in HIV-infected persons

Humoralni odgovor na anti-COVID-19 imunizaciju i SARS-CoV-2 infekciju kod osoba inficiranih HIV-om

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Abstract

Background/Aim. At the beginning of the coronavirus disease 2019 (COVID-19) pandemic, human immunodeficiency virus (HIV)-infected persons (HIP) were considered to be at an increased risk of more severe forms of the disease. Although vaccination of HIP is deemed essential, data on the humoral response to both infection and vaccination in this population are inconsistent, particularly when comparing different vaccine types. The aim of this study was to examine factors that could influence severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) anti-spike protein antibody titers in HIP after vaccination and/or exposure to the virus. **Methods.** The study included all HIP who came for routine check-ups to the Center for HIV/AIDS of the University Clinical Center of Vojvodina, Serbia, from April to December 2022 and who had received at least two doses of the vaccine or had a positive history of COVID-19. Data on age, duration of antiretroviral therapy (ART), nadir and current $CD4^+$ and $CD8^+$ T-cell counts, and type of vaccine were collected from medical records and the national database. Immunoglobulin G (IgG) antibodies against SARS-CoV-2 spike protein were determined in the sera of HIP using the AdviseDx SARS-CoV-2 IgG II assay. **Results.** The research included 226 HIP with undetectable viremia, in 96.3% of cases, the CD4 T-lymphocyte count was over 350 cells/mm^3. Out of 171 HIP who received at least two doses of a vaccine, 64 (37.4%) were both vaccinated and had COVID-19 and 107 (62.6%) were vaccinated and had no evidence of COVID-19. Among the vaccinated participants, 62% received three doses and 38% received two vaccine doses. Regarding the type of vaccine, 59.6% of participants received a messenger ribonucleic acid (mRNA) vaccine, 25.1% an inactivated vaccine, and 15.3% received a vector vaccine. A better humoral response was observed in the mRNA compared to the inactivated vaccines and in three compared to two doses in the case of mRNA vaccines. Age and duration of ART negatively correlated with antibody titers, while the number of CD8 T-cells had a positive correlation. **Conclusion.** The study showed the immunogenicity and safety of full vaccination against COVID-19 in HIP with any of the available vaccines.

Key words:
covid-19; hiv; immunity, humoral; immunoglobulin g; sars-cov-2; t-lymphocytes; vaccination; vaccines.

Apstrakt

Uvod/Cilj. Na početku pandemije izazvane koronavirusom 2019 (*coronavirus disease 2019* – COVID-19), smatralo se da su osobe inficirane virusom humane imunodeficijencije (HIV) u većem riziku od razvoja težih formi ove bolesti. Iako se vakcinacija HIV-inficiranih smatra neophodnom, podaci o humoralnom odgovoru na infekciju i vakcinaciju u ovoj populaciji su nedosledni, posebno kada se porede različite vrste vakcina. Cilj ove studije bio je da se istraže faktori koji bi kod osoba inficiranih HIV-om mogli da utiču na titar antitela specifičnih za *spike* protein koronavirusa 2 izazivača teškog akutnog respiratornog sindroma (*severe acute respiratory syndrome coronavirus 2* – SARS-CoV-2) nakon vakcinacije i/ili nakon izlaganja virusu. **Metode.** U studiju su bile uključene sve HIV-inficirane osobe koje su došle na rutinski pregled u Centar za HIV/AIDS, Univerzitetskog kliničkog centra Vojvodine, Srbija, od aprila do decembra 2022. godine i koje su primile najmanje dve doze vakcine i/ili su preležale COVID-19. Podaci o starosti, trajanju antiretrovirusne terapije (ART), najnižem i trenutnom broju $CD4^+$ i $CD8^+$ T-ćelija i podaci o tipu vakcine prikupljeni su iz medicinske dokumentacije i nacionalne baze podataka. Imunoglobulin G (IgG) antitela protiv SARS-CoV-2 *spike* proteina određivana su u serumima osoba inficiranih HIV-om

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korišćenjem AdviseDx SARS-CoV-2 IgG II testa. **Rezultati.** U istraživanje je bilo uključeno 226 HIV-inficiranih osoba sa nedetektabilnom viremijom, u 96,3% slučajeva, broj CD4 T-limfocita bio je preko 350 ćelija/mm^3. Od 171 ispitanika koji su primili najmanje dve doze vakcine, 64 (37,4%) je bilo i vakcinisano i imalo COVID-19 a 107 (62,6%) je bilo samo vakcinisano i nije imalo COVID-19. Među vakcinisanim ispitanicima, tri doze primilo je 62%, a njih 38% je primilo dve doze vakcine. Kada je u pitanju tip vakcine, 59,6% primilo je vakcinu na bazi informacione ribonukleinske kiseline (*messenger ribonucleic acid* – mRNA), 25,1% inaktivisanu vakcinu, a 15,3% vektorsku vakcinu. Bolji humoralni odgovor je pokazan u slučajevima mRNK vakcine u odnosu na inaktivisanu vakcinu i kod onih koji su primili tri doze u odnosu na dve u slučaju mRNK vakcina. Godine starosti i trajanje ART su bili u negativnoj korelaciju, a broj CD8 T-ćelija u pozitivnoj korelaciji sa titrima antitela. **Zaključak.** Studija je pokazala imunogenost i bezbednost potpune vakcinacije protiv COVID-19 kod osoba inficiranih HIV-om bilo kojom od dostupnih vakcina.

Ključne reči:
covid-19; hiv; imunitet, humoralni; imunoglobulin g; sars-cov-2; limfociti t; vakcinacija; vakcine.

Introduction

In late 2019, a new virus spread rapidly worldwide, resulting in a global pandemic. The virus was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease it caused was named coronavirus disease 2019 (COVID-19). Early in the pandemic, human immunodeficiency virus (HIV)-infected persons (HIP) were defined as a population with vaccination priority. Large cohort studies from the UK, the USA, and South Africa, including data reported to the World Health Organization from across the world, identified a higher risk of death and hospitalization from COVID-19 in this population [1–6]. Even so, many questions on humoral response to infection and vaccination in HIP remain unanswered.

Traditionally considered immunodeficient, HIP are a very heterogeneous population, with numerous factors influencing humoral response to vaccines and infections. There are distinct challenges in mounting effective immune responses in HIP, particularly in response to vaccination. The primary deficiency in HIP is the depletion of CD4$^+$ T-cells, which are critical for orchestrating the immune response. Not only does this T-cell deficiency affect cellular immunity, but it also impairs the function of B cells, which are crucial for producing antibodies in response to infections and vaccinations, including those against SARS-CoV-2[5].

In the pre-registration studies of messenger ribonucleic acid (mRNA) and vector vaccines against COVID-19, HIP were very poorly represented in the studied populations [7, 8]. The effectiveness and safety of inactivated vaccines were not tested before their use in HIP, so the recommendations were based on data from previously used inactivated vaccines in this population.

The response to COVID-19 in Serbia involved a combination of public health measures, healthcare system adaptation, government policies, and international collaboration. Serbia's approach evolved throughout the pandemic as the country faced successive waves of infection, adjusting strategies to curb the spread of the virus and mitigate its impact on society and the economy. By March 2021, four different vaccines became available for Serbian citizens: mRNA vaccine Pfizer-BioNTech/BNT162b2 (Comirnaty®), inactivated vaccine Sinopharm/BBIBP-CorV (Vero Cell®), and two vector vaccines Gam-COVID-Vac (Sputnik V®) and Oxford/AstraZeneca ChAdOx1-S/nCoV-19, AZD1222 (Vaxzevria®). All of the vaccines were also available for HIP, with the choice of vaccine left to the patients or their caregivers, with no clear protocols for their use in this population. To our knowledge, all three vaccine types against COVID-19 (inactivated, vector, and mRNA) are hardly ever offered to HIP from a single cohort.

The aim of this study was to examine factors influencing humoral response to vaccination against COVID-19 and natural exposure to the SARS-CoV-2 in the cohort of HIP.

Methods

We conducted a cross-sectional, observational study on 226 participants at the Center for HIV/acquired immunodeficiency syndrome (AIDS), Clinic for Infectious Diseases, University Clinical Center of Vojvodina, Novi Sad, Serbia. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Novi Sad (No. 01-39/189/1, from March 31, 2022).

All HIP who had routine check-ups between April 1 and December 30, 2022, and either received at least two doses of the anti-COVID-19 vaccine and/or were previously diagnosed with COVID-19 were included in the study. The exclusion criteria were hepatitis B and/or C co-infections and unwillingness to participate in the study. All HIP who met the criteria signed the informed consent and were then included in the study. Remnant serum samples were collected from all the participants who underwent routine outpatient laboratory testing for the measurement of immunoglobulin G (IgG) antibody titer.

Relevant data on the HIV infection were collected using participants' medical records. The data included their current age, estimated duration of the HIV infection, nadir and current CD4$^+$ and CD8$^+$ T-cell counts, and current polymerase chain reaction (PCR) HIV RNA viral load. Data on vaccine type and date of the vaccination against COVID-19 were collected using the national database. Data on events associated with adverse effects of the vaccines were collected from the participants in a short interview during their visit to

the Clinic. Data on thrombosis after vaccination were collected from the medical records of HIP.

Which of the available vaccines will HIP receive is based on the individual's decision after obtaining advice from a general practitioner or their HIV physician. At the time of the study, HIP were recommended to receive three doses of the vaccine, i.e., primary series plus a booster.

Determination of IgG antibodies against SARS-CoV-2 spike protein was performed using the AdviseDx SARS-CoV-2 IgG II assay [9]. The assay is a chemiluminescent microparticle immunoassay (CMIA) intended for the qualitative and semi-quantitative detection of IgG antibodies to the receptor-binding domain of the S1 subunit of the spike protein of SARS-CoV-2 in serum and plasma. The resulting chemiluminescent reaction was measured as a relative light unit, which was then translated into antibody concentration in arbitrary units (AU/mL). Samples with > 12 AU/mL, 10–12 AU/mL, and < 10 AU/mL were considered positive, indeterminate, and negative for IgG, respectively.

Statistical analysis data was performed using SPSS 20.0 software. Frequencies and percentages were used to describe and analyze the sample in order to represent the delineation of certain categories or answers. Descriptive statistical methods were used to measure central tendencies (arithmetic mean), variability (standard deviation), and extreme values (minimum and maximum) of the analyzed numerical features.

Before proceeding with further statistical analyses, the distribution of the scores of the applied scales was verified. Transformation of the predictor and criterion variables was then performed using normalization and standardization, given that the initial distributions significantly deviated from the normal. In further analysis, the *t*-test was used to compare means between two groups, and analysis of variance (ANOVA) was used to compare means across three or more groups. Spearman correlation was used to assess relationships between continuous variables.

Results

Demographic data

Out of 550 HIP undergoing treatment, 226 (41.2%) were included in the research. The average age of the participants was 41.3 years (Table 1).

All participants were on antiretroviral therapy (ART) and had undetectable viremia for at least six months prior to this study. Most participants (61%) were on integrase strand transfer inhibitor (INSTI)-based treatment, 30% were on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART, while 9% were on protease inhibitor (PI)-based treatment. HIP who were on unconventional or salvage treatments were not included in the study. The average duration of ART was 5.6 years. Regarding the CD4+ T-cell count, 19.7% of the participants had previously AIDS, while 48.0% of the subjects had a nadir $CD4^+$ T-cell count of less than 350 cells/mm^3. The current $CD4^+$ T-cell count was between 200 and 350 cells/mm^3 in only 3.7% of the subjects, while all other subjects (96.3%) had a CD4 T-lymphocyte count over 350 cells/mm^3. The current CD4/CD8 ratio was above 1.0 in 32%, while in the rest of the participants, this ratio was below 1.0, potentially indicating persistent inflammation in these participants.

Regarding ways of transmission, all the subjects included in the study have been infected by the sexual route, and none were infected due to intravenous drug use.

Vaccination against COVID-19

Of 226 participants in the study, 171 (75%) had been vaccinated with at least two vaccine doses. All vaccinated participants received a homologous primary series of one vaccine type. In individuals who received booster doses, the same type of vaccine was used as in the primary series.

Out of all vaccinated participants, 64 (37.4%) were both vaccinated and previously diagnosed with COVID-19, and 107 (62.6%) were vaccinated but were not previously diagnosed with COVID-19 (Table 2). The most commonly received vaccine, in 59.6% of vaccinated participants, was the mRNA. The second most commonly received was the inactivated vaccine, taken up by 25.1% of participants, while the rest (15.3%) received one of the two available vector vaccines. According to the results of the interviews and medical records, no significant adverse effects were observed with any type of vaccine. In the group analysis, there was no statistically significant difference in age, ART duration, and immunological parameters among the vaccine type groups.

Regarding the number of doses, 62% of vaccinated HIP received three doses and 38% received two vaccine doses (Table 2). Full vaccination with three vaccine doses was

Table 1

General characteristics of the cohort

Parameters	Mean ± SD	Min–Max
Age (years)	41.3 ± 12.0	20–74
Nadir $CD4^+$ T-cell count (cells/mm^3)	401.3 ± 298.4	3–1,514
Nadir $CD8^+$ T-cell count (cells /mm^3)	1,147.7 ± 709.3	149–8,299
Current $CD4^+$ T-cell count (cells /mm^3)	1,075.5 ± 991.7	270–14,422
Current $CD8^+$ T-cell count (cells /mm^3)	1,351.8 ± 484.0	259–2,200
Current CD4/CD8 ratio	0.8 ± 0.3	0.2–2.51
Duration of ART (years)	5.5 ± 4.5	0.5–23
SARS-CoV-2 anti-spike IgG titer (AU/mL)	8,832.1 ± 29,527.3	9.0–42,000

SD – standard deviation; ART – antiretroviral therapy; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2; IgG – immunoglobulin G; AU – arbitrary units; min – minimum; max – maximum.

Table 2

Comparison of variables based on the number and type of the received vaccine and registered COVID-19

Variables	Registered COVID-19	n	Age (years)	Years of ART	Nadir CD4 (cells/mm^3)	Nadir CD8 (cells/mm^3)	IgG anti-spike antibody titer (AU/mL)
Three vaccine doses ‡							
mRNA	yes	30	41.5	5.9	391.4	1,205.5	16,526.3 ± 13,838.3*†
	no	28	43.1	6.0	404.0	1,441.1	12,260.7 ± 1,1474.0
inactivated	yes	7	40.0	7.3	320.1	945.1	4,257.5 ± 4,004.8*
	no	23	49.1	8.1	263.6	1,022.7	7,315.2 ± 6,599.0
vector	yes	5	39.0	5.0	481.2	1,229.0	11,411.5 ± 11,194.3
	no	13	44.9	5.9	430	1,091.2	9,714.0 ± 9,606.0
Two vaccine doses							
mRNA	yes	14	35.5	4.8	533.0	998.9	5,534.6 ± 2,850.5†
	no	30	36.9	3.6	494.3	1,083.3	4,763.8 ± 4,344.1
inactivated	yes	4	41.7	4.2	584.0	1,562.5	7,507.2 ± 2,995.7**
	no	9	36.8	4.1	432.1	946.0	1,812.5 ± 1,703.0**
vector	yes	4	40.5	4.25	434.0	970.5	2,047.2 ± 1,784.2
	no	4	33.3	2.3	610.0	1,242.3	10,497.0 ± 8,786.0
Not vaccinated‡	yes	55	41.8	5.1	366.9	1,002.8	1,330.5 ± 1,765.1

n – number of participants; *signifficant difference between the three-dose mRNA vaccine group vs. the three-dose inactivated vaccine group ($p = 0.04$); †signifficant difference between the three-dose mRNA vaccine group vs. the two-dose mRNA vaccine group ($p = 0.005$); **signifficant difference between the two-dose inactivated vaccine with no registered COVID-19 group vs. the two-dose inactivated vaccine with registered COVID-19 group ($p = 0.0016$); ‡signifficant difference between all groups vaccinated with three doses vs. the non-vaccinated group ($p < 0.005$).
COVID-19 – coronavirus disease 2019; mRNA – messenger ribonucleic acid; ART – antiretroviral therapy; AU – arbitrary units; IgG – immunoglobulin G.
All values are given as mean ± standard deviation or number.

achieved in 56.8% of individuals in the mRNA group, in 60.0% of the vector vaccine group, and in 69.7% of the inactivated group.

In the group analysis, booster dose was more likely to be received by HIP previously diagnosed with AIDS, who were over 40 years of age and on ART for more than 5 years ($p = 0.05$).

In total, 55 (24.3%) participants included in the study had not been vaccinated against COVID-19. There were no statistically significant differences between vaccinated and unvaccinated participants in age, ART duration, nadir or current CD4$^+$ and CD8$^+$ T-cell counts, or current CD4/CD8 ratio.

SARS-CoV-2 anti-spike IgG antibody titer

The lowest values of antibody titers were seen in persons who had COVID-19 and were not vaccinated against the disease. Significant differences in antibody titers were seen among unvaccinated HIP compared to all vaccinated HIP with three doses, regardless of the type of vaccine ($p < 0.005$).

The highest values of titers were seen in HIP who received the mRNA vaccine. In individuals who both had COVID-19 and received a vaccine, the titer in the mRNA vaccine group was statistically higher than that in the inactivated vaccine group ($p = 0.04$). However, no differences were found between the mRNA group and the vector vaccine group. In the analysis of HIP who were vaccinated but did not have COVID-19, the humoral response did not differ among the vaccine types.

Regarding the number of vaccine doses, the greatest benefit from the booster was found in the mRNA vaccine group. In this group, there was a great difference in antibody titers between the persons who received a booster compared to the persons who received two vaccine doses ($p = 0.005$). No such boosting effect was seen in the remaining two types of vaccines. The greatest effect of COVID-19 on antibody titer was observed in the inactivated vaccine group. In this group, there was a statistically significant difference in the titers between the persons who had and did not have the diseases ($p = 0.0016$).

In all vaccinated participants, antibody titer had a slight but significant negative correlation with age ($r = -0.90$, $p = 0.04$). The correlation between age and antibody titer was stronger in participants who were both vaccinated against and diagnosed with COVID-19 ($r = -0.27$, $p = 0.036$). ART duration negatively correlated with antibody titer in vaccinated individuals who were also diagnosed with COVID-19 ($r = -0.39$, $p = 0.02$). The correlation was absent between those who were vaccinated but never infected, and vice versa.

Nadir and current CD4$^+$ T-cell count, as well as nadir and current CD4/CD8 ratio, did not correlate with antibody titers in vaccinated participants. Furthermore, there were no statistically significant differences in antibody titers between individuals whose nadir CD4$^+$ T-cell count was below 200 cells/mL^3 and those who were never immunocompromised. On the other hand, nadir CD8 levels had a positive impact on antibody titers.

The time since the last vaccine dose was, on average, 96 days (min 60, max 150). The time since COVID-19 in

vaccinated HIP was, on average, 94 days (min 18, max 206). Neither time period correlated with antibody titers.

Similar results were observed in the unvaccinated HIP group. The antibody titer in this group did not correlate with the time since COVID-19 diagnosis (mean 109, min 25, max 256). In addition, antibody titers did not correlate with other factors, such as nadir and current $CD4^+$ and $CD8^+$ T-cell counts, age, and ART duration.

Discussion

Based on previous experience with other causes of atypical pneumonia, such as influenza, SARS-CoV-2 infection was initially considered especially dangerous for HIP. As efforts to combat the virus intensified, the development and deployment of vaccines emerged as crucial actions in controlling the spread and mitigating the impact of COVID-19. In this study, we compared humoral responses in HIP who had suppressed viral replication at the time of study with good immunological status but who received different types of anti-COVID-19 vaccine and a number of doses.

Unlike HIV infection, which is fatal in the absence of ART, COVID-19 has a variable clinical course, especially in immunocompromised individuals [10, 11]. Although SARS-CoV-2 infection was mild in the majority of cases, there have been reports of poor outcomes due to the development of acute respiratory distress syndrome. In our study, the poorest humoral response to the infection was in HIP who were not vaccinated, which supports the concern that the immune response to SARS-CoV-2 may be partly inadequate in this population.

Due to widely available ART, HIP are an aging population. One of the factors that stood out as a negative predictor for poorer humoral response to vaccines in our study was advanced age. Age negatively correlated with antibody titers in all vaccinated participants in our study. However, the correlation was not present in those who developed humoral immune response through natural exposure to the virus. This result is not surprising, as previous studies identified advanced age as a significant negative modulator of humoral response following two-doses of anti-COVID-19 vaccine, warranting a three-dose vaccination regimen in older individuals [12, 13].

Many studies examined the effect of CD4 T-cell count on immunogenicity in HIP. In a review by Søndergaard et al. [13], a lower serological response was associated with HIP with a lower $CD4^+$ T-cell count in 26 out of 59 studies (44%). Similarly, in the meta-analysis by Zhou et al. [14], the seroconversion was 4.6 times higher in HIP with higher $CD4^+$ T-cell counts than in HIP with lower CD4 counts. We did not find any correlation between $CD4^+$ T-cell count and antibody titer, although none of the patients had a current $CD4^+$ T-cell count below 200 cells/mL^3.

HIV infection is characterized by a profound disruption of the immune system, and even in HIP with fully suppressed viral load, up to 30% of patients will suffer incomplete immune recovery [15, 16]. Therefore, it was essential to investigate T-cell count in relation to antibody titers in the participants of this study. There was no correlation between $CD4^+$ T-cell count and CD4/CD8 ratio and the antibody titer levels, regardless of the type of vaccine. However, we found that the nadir $CD8^+$ T-cell count correlated with the level of humoral response to vaccination, indicating the importance of these elements in the cellular response to immunization. We did not find any studies that specifically examined nadir CD8 as a predictor of humoral response to anti-COVID-19 vaccines. Nevertheless, there is plenty of data on the importance of $CD8^+$ T-cell response to pathogens and vaccination. Activated $CD8^+$ T-cells can induce apoptotic death of virus-infected cells by producing tumor necrosis factor-alpha and interferon-gamma (IFN-γ) [17–19]. Early mRNA vaccine studies revealed that all arms of adaptive immunity respond to immunization, including $CD8^+$ T-cells that produce IFN-γ [20–22]. Recent studies suggest that IFN-γ production from $CD8^+$ T-cells enhances cellular and humoral immune responses following immunization [23, 24]. Based on these and similar studies, it is indicated that individuals with higher nadir CD8+ T-cell counts may have a better immune response, including that toward vaccines.

Regarding the number of doses, more than half of the participants (62%) received three doses of the vaccine. Based on the results of our study, there was a significant increase in antibody titer after the third dose in the case of the mRNA vaccine. We did not find similar boosting effects in the other two vaccine types. Still, in agreement with many previous studies and national recommendations, we would also recommend giving three doses of the vaccine [25–27].

Regarding the type of vaccine, at the time of vaccination of our cohort, there were no specific guidelines on which type of vaccine is better for HIP. The data were just coming out on the supreme immunogenicity of the mRNA vaccine in the general population, but some HIP were hesitant to receive the novel type of vaccine. No patients reported serious adverse effects with any of the vaccines, and all patients seroconverted. Most participants (59.6%) received the mRNA vaccine, a quarter of the participants received the inactivated vaccine (25.1%), and 15.3% received the vector vaccine. We showed a statistically significant difference in antibody titers between the mRNA vaccine compared to the inactivated vaccine in persons who previously had COVID-19.

The favorable humoral response to the mRNA vaccine found in our study is in accordance with most real-world studies on vaccination in HIP. Several meta-analyses [14, 27, 28] clearly showed the supreme immunogenicity of the mRNA vaccine in HIP.

A limitation of our study was its cross-sectional nature. As HIP received the last vaccine dose 3 to 6 months before IgG titer measurement, a follow-up study of titer values might show the immunogenicity of different types of vaccines and the degree of long-term protection conferred by different types of vaccines. Another limitation of the study was the great variability of the antibody titers, which clearly shows that individual variation in humoral response to vaccination goes far beyond the factors investigated in this study.

Conclusion

All available vaccines against coronavirus disease 2019 have led to seroconversion in our cohort. Although there was significant variation from the mean in achieved antibody titers, it appears that age and time since introduction to antiretroviral therapy may be factors that have a negative influence on humoral response to immunization. Attention is needed in older patients and those who have been on antiretroviral therapy for a long time, who may therefore need more booster doses and more frequent antibody measurements. Our findings are in agreement with general recommendations for the safe and effective use of the messenger ribonucleic acid vaccine in persons infected with human immunodeficiency virus.

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