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Case Report

CASE REPORTS ON COVID-19 OUTCOMES DURING THE PANDEMIC IN PATIENTS WITH WELL-MANAGED HIV INFECTION IN LATVIA

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global pandemic with serious implications and open questions for all areas of medicine, including immunocompromised patients. In Latvia, as of the end of 2022, 229 new cases of HIV were registered, reflecting an incidence rate of 12.2 per 100,000 people. Despite the fact that immunocompromised patients are at risk of poor outcomes of COVID-19, there is currently no evidence that clinical manifestations of COVID-19 in people living with HIV (PLWH) differ from those in the general population, provided these patients have well-controlled immune status (CD4+ count > 200 and undetectable viral load). We report two cases of COVID-19, specifically the Delta variant, in male patients with well-controlled HIV infection who had received three vaccine doses against COVID 19. Both patients fully recovered within one week without complications, requiring no specific treatment. Considering the current published data and our observations, it can be assumed that the course of COVID-19 in vaccinated well-controlled HIV patients does not differ from the typical clinical manifestations of COVID-19 in the general population. It is necessary to decrease vaccine hesitancy among PLWH, as COVID-19 vaccination is a crucial measure to safeguard this segment of the population against poor outcomes of COVID-19 such as hospitalisation, the risk of long-term health problems, severe disease, and death).

Keywords: *immunodeficiency, clinical manifestations, outcome, vaccine.*

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has triggered a global pandemic, presenting significant challenges and numerous difficulties across all areas of healthcare, especially for patients with a suppressed immune system. The number of new COVID-19 cases continues to increase daily among all groups of patients.

At the end December 2023, there had been more than 772 million confirmed cases of COVID-19, with over 6 million reported deaths worldwide to WHO. In Latvia, more than 981 thousand confirmed cases and 6609 deaths have been reported (WHO COVID-19 Dashboard, 2023).

At the same time, the COVID-19 pandemic is becoming a big problem while also the ongoing HIV epidemic has started to grow, despite global solutions that were engineered to stop the HIV epidemic.

At the end of 2022, 39 million (33.1–45.7 million) people were living with HIV (PLWH), and 680,000 (480,000–1.0

million) people died from HIV-related causes, with approximately 1.7 million newly infected adults and children (UNAIDS, 2022).

In 2022, the WHO European Region reported 110,486 new HIV diagnoses, corresponding to a rate of 12.4 per 100,000 population. Cyprus (24.1) and Estonia (18.8) had the highest HIV rates per 100,000 population (ECDC, 2022).

Latvia registered 229 new cases of HIV in 2022 with an incidence rate of 12.2 per 100,000 people (SPKC, 2022).

In 2022, approximately 86% of people with HIV worldwide were aware of their HIV status, while the remaining 14% were unaware (HIV.gov, 2022).

Additionally, as of the end of 2022, 29.8 million people worldwide with HIV (75%) were receiving antiretroviral therapy (HAART).

As is known, regular intake of antiretroviral therapy (ART) has significantly contributed to the fact that the life expectancy of PLWH is comparable to that of the general population.

Presently, effective ART enables PLWH to age with their disease, and the leading cause of death among HIV-infected individuals is more likely to result from an HIV-associated non-AIDS condition (Ball *et al.,* 2014). In high-income settings, the primary health concerns for adult PLWH today are also diseases that are not directly associated with HIV (Martínez-Sanz *et al*., 2022).

Increased aging of PLWH is associated with increased risk of age-related chronic illnesses, including cardiovascular diseases, chronic obstructive pulmonary diseases, cancers, chronic kidney disease, and diabetes mellitus (Webel *et al.,* 2021).

Various studies indicate that individuals from the general population with comorbidities face a higher risk of adverse outcomes of COVID-19 compared to those without comorbidities (Danwang *et al.,* 2022). PLWH may also be susceptible to more severe consequences of COVI-19 due to shared demographic and medical characteristics that are recognised as risk factors for severe COVID-19 disease (Fung *et al.*, 2020). However, the information regarding the association between HIV and adverse outcomes in patients with COVID-19 remains conflicting and subject to debate (Fung *et al.*, 2020; Sigel *et al.,* 2020; Plummer *et al.,* 2021; Danwang *et al.,* 2022; Jakharia *et al.,* 2022).

There have been multiple published case series from around the world describing the course of COVID-19 disease in PLWH. 75–100% of these cases were in patients with well-controlled HIV infection (a CD4 count > 200 cells/μl and undetectable viral load) (Fung *et al.*, 2020).

According to the research by Fung *et al*., the current data on PLWH were not conclusive regarding whether HIV imparts a higher risk of severe disease of COVID-19 (Fung *et al.*, 2020).

Despite the fact that patients with a suppressed immune system are at risk of poor outcomes of COVID-19 (Jakharia *et al.,* 2022), there is no evidence that clinical manifestations of COVID-19 in PLWH differ from those of the general population, provided that these patients have a well-controlled immune system) (CD4+ count 200 and undetectable viral load) (Cooper *et al*., 2020).

According to the research by Antinori *et al*. (2022), cell-mediated and humoral immune responses to mRNA vaccines were significantly reduced in PLWH with a CD4 count < 200 cells/mm^3, while those with a CD4 > 500 cells/mm^3 showed comparable immune response to matched HIV-negative controls. Further data from this same cohort, when tested at a median follow-up of 175 days from the second vaccine, demonstrated significantly lower rates of detectable neutralising antibodies in those with a CD4 count < 200 cells/mm^3 compared to those with higher counts (Antinori *et al.*, 2022).

A meta-analysis of 13 studies including 13,016 HIV-infected individuals with COVID-19 and 1,744,014 HIV-uninfected individuals with COVID-19, showed that HIV did not significantly increase the likelihood of experiencing severe COVID-19 (OR: 1.28; 95% CI 0.77–2.13) (Danwang *et al.,* 2022).

Many researchers agree that there are no differences in adverse outcomes associated with HIV infection for hospitalised COVID-19 patients compared with a demographically similar patient group (Sigel *et al.,* 2020).

The majority of the published literature has not supported that PLWH have a higher risk for aggravation or death from COVID-19 than the general population (Ceballos *et al.*, 2021; Plummer *et al.,* 2021).

According to the meta-analysis of prevalence information based on 38 studies the pooled prevalence of HIV among COVID-19 patients was 26.9‰ (95% confidence interval [CI] 22.7–31.3) and the pooled prevalence of HIV among studies conducted on hospital records was 24.6‰ (95% CI 20.4–29.1, 33) (Danwang *et al.,* 2022).

Another conclusion, suggesting that PLWH are more likely to be hospitalised and face a higher risk of mortality compared to persons without diagnosed HIV, has been drawn by different groups of scientists in New York and the UK (Tesoriero *et al.,* 2021; Bhaskaran *et al*., 2021) (Fig. 1). Similarly, in Spain, HIV-infected patients with COVID-19 presented a higher prevalence of critical illnesses compared to those without HIV (Vallée *et al.,* 2021).

A group of scientists from Chile found that PLWH who developed severe COVID-19 did not differ in medical factors and comorbidities from those PLWH who had a more benign course of the disease (Ceballos *et al.*, 2021). Additionally, PLWH who died had a higher prevalence of some comorbidities such as hypertension and cardiovascular disease than patients with HIV who have survived (Ceballos *et al.*, 2021).

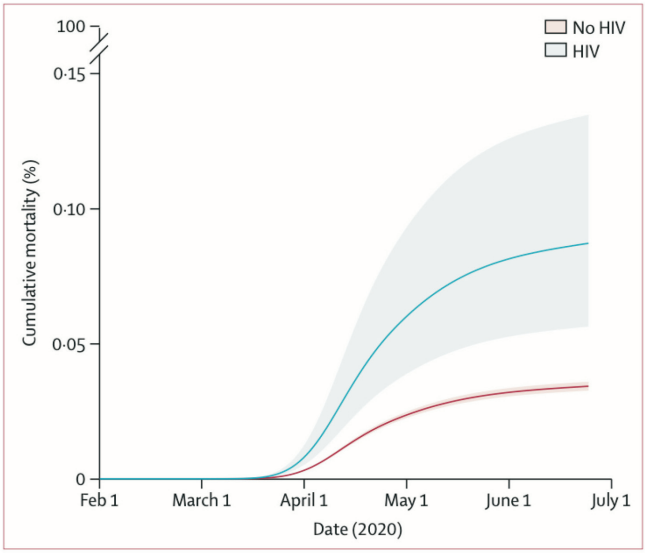

Fig. 1. Cumulative COVID-19 mortality by HIV status with 95% CI, standartised to covariate distribution of the HIV group (republished from Bhaskaran K *et al*., 2021).

According to information from the U.S. CDC, people with well-controlled HIV have the same risk of developing COVID-19 as HIV-negative people. However, the risk for PLWH experiencing serious COVID -19 outcomes is greatest for those with a low CD4 T-cell count who are not on effective HAART treatment (Plummer *et al.,*2021; cdc.gov, 2022).

There is no doubt that HIV virus is one of the most common causes of a suppressed immune system around the world. Many PLWH are in the age group over 50, have cardiovascular diseases, metabolic disorders, and other comorbid pathologies that are risk factors for severe outcomes of COVID-19; therefore, special attention should be focused on COVID-19 vaccination.

Collection of statistical data on the proportion of PLWH among patients with COVID-19 for the years of the pandemic in Latvia is currently in progress.

In December 2020, the first vaccine dose was administered. If, in 2021, only 27% of the world's population were fully vaccinated (Rashedi *et al*., 2021), nowadays, approximately 80% of the population (about five billion people) are fully vaccinated, and more than 450 million people who are partly vaccinated (have received at least one dose of the available COVID-19 vaccines) (Ourworldindata.org, 2023). A major part of those who refused to get vaccinated report concerns about the safety of the new COVID-19 vaccines (Vallée *et al.,* 2021) (Fig. 2).

PLWH may need to be a priority for COVID-19 vaccination (Vallée *et al.,* 2021). There are no data to suggest that the vaccines are not safe and effective for PLWH, including adolescents between 12 and 15 years (Plummer *et al.,* 2021). Costiniuk CT. and other authors found that COVID-19 vaccines are safe and well tolerated in PLWH.

Both HIV-1 and SARS-CoV-2 infection share CD4+ T cell loss in association with disease outcome and immunodeficiency (Peng *et al*., 2020).

HIV-positive patients can receive the COVID-19 vaccine while they do not have other conditions that would exclude them (e.g severe or immediate allergic reaction to a vaccine component) (Plummer *et al.,* 2021). The majority of PLWH obtained a detectable antibody response at 3 and 6 months following the 2nd dose and one month following a 3rd or booster dose (Costiniuk *et al.*, 2023).

WHO indicates that expected protection obtained from COVID-19 vaccines may be weaker in PLWH, especially for those individuals with low CD4+ counts (less than 100) (Plummer *et al.,* 2021). However, the overall benefits of receiving any of the authorised COVID-19 vaccines in a pandemic situation currently outweigh the potential risks, even for people with impaired immune systems (Plummer *et al.,* 2021).

According to recent studies evaluating immune responses to a COVID-19 vaccine in immunocompromised patients, results varied depending on the population groups such as haemodialysis patients, cancer patients, transplant recipients or patients treated with immunosuppressors (Nault *et al.,* 2022).

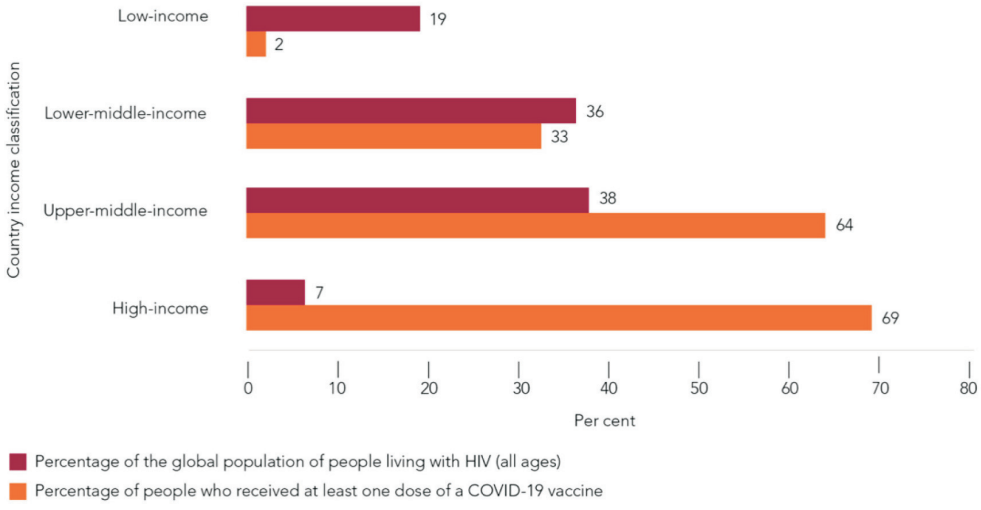

Fig. 2. Distribution of the population covered by at least one dose of a COVID-19 vaccine (as of 5 October 2021), compared to the distribution of people living with HIV (all ages), by country income classification (republished from UNAIDS, 2021).

To date, there is no evidence of increased vaccine-related adverse events in PLWH, compared to the general population (Gong *et al*., 2022).

CASE DESCRIPTION

We report two cases of COVID-19, Delta variant, in male patients with well-controlled HIV infection, fully vaccinated with three vaccine doses against COVID-19 in 2021.

The first patient was a 39-year-old Caucasian male, MSM, who worked out of the office. He was diagnosed with HIV I A III stage in 2013. From his medical history, he was diagnosed with Kaposi's sarcoma in 2013, and currently, the patient is in remission after successful therapy. The patient has a body mass index of 32, suffers from arterial hypertension, and regularly takes antihypertensive medications. He has been receiving ART therapy for the last twelve years, which he is committed to and tolerates well. The patient was diagnosed with HIV I C III, blood examination showed a CD4+ cell count of 390 cells/mm^3, and the immune status has been relatively stable for the last nine years. HIV RNA was not detected since 2015. The patient was not diagnosed with other immunosuppressive diseases such as hepatitis B, C, tuberculosis, etc. COVID-19 was suspected in December 2021 and was confirmed by a positive RT-PCR through nasopharyngeal swab (Delta variant) due to symptoms such as subfebrile temperature for five days, nasal congestion, and sore throat. The patient received nonspecific treatment for symptoms, and no specific treatment was required. He fully recovered after seven days without complications. Before the onset of COVID -19, this patient had received three vaccine doses in 2021. In December 2023, the patient experienced nonspecific symptoms again, and SARS CoV-2 was confirmed by a positive home test. No therapy was required due to the mild course of the disease. The patient currently receives annual booster vaccinations.

The second patient was a 40-year-old Caucasian male, MSM, an out of office worker, who was diagnosed with HIV I A II in 2017. The patient had a history of Lues II recens (December 2021) with appropriate therapy, and no other underlying chronic diseases. He has been under ART regimen for the last seven years. He has well-controlled immune status (CD4+cell count of 650 cells/mm3, HIV RNS — not detected from 2019), hepatitis B, C, and tuberculosis were not detected. The patient was fully vaccinated with three doses of COVID-19 vaccine in 2021. In December 2021, the patient experienced nonspecific respiratory symptoms, subfebrile fever, and this included a loss of sense of smell. SARS CoV-2, Delta variant, was confirmed by a positive RT-PCR test through a nasopharyngeal swab. The patient fully recovered after six days without specific treatment or complications. In November 2023, COVID-19 was diagnosed again using a home test, but the disease was mild and did not require any specific treatment. The patient continues to receive the annual booster vaccine.

CONCLUSION

Based on the currently available data and our findings, we can assume that the course of COVID-19 in well-controlled HIV patients who have been vaccinated does not differ from the typical clinical manifestations of COVID-19 in the general population.

However, many HIV patients do not initiate antiretroviral therapy (ART) immediately, even when eligible, leading to excess morbidity, mortality, and viral transmission (Ahmed *et al.,* 2018).

Recent research indicates that decisions to delay ART initiation are influenced by factors such as feeling healthy, low social support, gender norms, HIV stigma, and challenges in translating good intentions into actions. Other contributing factors include high care-seeking costs, concerns about confidentiality, low-quality health services, recommended lifestyle changes, and incomplete knowledge of treatment benefits (Ahmed *et al.* 2018).

The demand for ART could potentially increase if patients were provided with more information about the health and prevention benefits of early ART and the reduced toxicity profile of existing regimens (Ahmed *et al.* 2018).

In Latvia, a significant number of patients from specific social groups (such as those considered asocial, IVDU etc.) exhibit non-compliant with ART therapy. They may skip doses and apply it irregularly, taking the prescribed therapy with long interruptions. Therefore, there is a critical need to address vaccine hesitancy within this segment of the population. COVID-19 vaccination is an essential measure to protect these patients against poor outcomes of COVID-19, including hospitalisation, the risk of long-term health problems, severe disease, and death.

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ZIŅOJUMI PAR COVID-19 GADĪJUMIEM PANDĒMIJAS LAIKA PACIENTIEM AR LABI KONTROLĒTU HIV INFEKCIJU LATVIJĀ

Smagais akūtais respiratorais sindroms, ko izraisa koronavīruss 2 (SARS-CoV-2), ir izraisījis globālu pandēmiju ar nopietnām sekām un atstājis neatbildētus jautājumus visās medicīnas jomās, ieskaitot pacientu ar novājinātu imunitāti iesaisti. Latvijā 2022. gadā tika reģistrēti 229 jauni saslimšanas gadījumi (saslimstības rādītājs 12,2 uz 100 000 iedzīvotāju). Neraugoties uz to, ka pacienti ar novājinātu imūnsistēmu ir pakļauti lielākam Covid-19 riskam, nav pierādījumu, ka Covid-19 klīniskās izpausmes pacientiem ar novājinātu imūnsistēmu atšķiras no vispārējās populācijas, ja vien šiem pacientiem ir labi kontrolēts imūnsistēmas stāvoklis (CD4+ skaits 200 un nenosakāma vīrusa slodze). Mēs ziņojam par diviem Covid-19 gadījumiem, Delta vīrusa variantu, vīriešiem ar labi kontrolētu HIV infekciju, kuri bija pilnībā vakcinēti ar trim vakcīnas devām pret Covid-19. Šie pacienti pilnībā atveseļojās bez komplikācijām pēc vienas nedēļas, un viņiem nebija nepieciešama specifiska ārstēšana. Pamatojoties uz pašreiz publicētajiem datiem un mūsu iegūtajiem rezultātiem, var secināt, ka Covid-19 slimības gaita vakcinētiem pacientiem ar labi kontrolētu HIV infekciju neatšķiras no tipiskajām Covid-19 klīniskajām izpausmēm vispārējā populācijā. Nepieciešams mazināt vilcināšanos vakcinēties pacientu ar novājināto imūnsistēmu vidū, jo Covid-19 vakcinācija ir būtisks pasākums, lai pasargātu šo iedzīvotāju grupu no Covid-19 smagām sekām, ieskaitot hospitalizāciju, ilgtermiņa veselības problēmu risku, smagu saslimšanu un nāvi.