THE FEATURES OF HIV AND SARS-COV-2-COINFECTION IN A PANDEMIC

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COVID-19 is known to undertake a severe course in several groups of patients. The review presents the latest data on the main features of COVID-19 course in HIV patients. People living with HIV, have not been found to be at a higher risk for acquiring COVID-19 and the disease runs a similar course compared to the general population in HIV patients on continuous antiretroviral therapy (ART) with a suppressed viral load and CD4+-T-lymphocytes count > 200cells/μl. Fewer than expected HIV patients have been reported to be hospitalised, this leads to hypothesize that infection may be majorly asymptomatic in this group of patients owing to their weak immune response. The patient's use of ART might also explain the comparatively milder disease course of COVID-19 seen in patients with HIV/SARS-CoV-2 coinfection. While ART use cannot be considered to be a protective factor against contracting the SARS-CoV-2, researchers assume that the therapy could stabilize the immune response in coinfected patients and thus prevent progression of the disease to the severe forms.

Keywords: COVID-19, SARS-CoV-2, HIV, human immunodeficiency virus, antiretroviral therapy, HIV/SARS-CoV-2-coinfection, PLHIV

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ОСОБЕННОСТИ ТЕЧЕНИЯ СОЧЕТАННОЙ ИНФЕКЦИИ ВИЧ/SARS-COV-2 В УСЛОВИЯХ ПАНДЕМИИ

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Известно, что некоторые группы пациентов тяжело переносят COVID-19. В обзоре представлены последние данные об особенностях течения COVID-19 у пациентов, инфицированных вирусом иммунодефицита человека (ВИЧ). Установлено, что у людей с ВИЧ, находящихся на непрерывной антиретровирусной терапии (АРВТ), имеющих подавленную вирусную нагрузку и число CD4+-Т-лимфоцитов более 200 клеток/мкл, риск заражения и течение COVID-19 сопоставимы с таковыми в общей популяции. Пациенты с ВИЧ-инфекцией демонстрируют меньшую частоту госпитализаций, чем ожидалось, что предположительно может быть связано с бессимптомным течением COVID-19 на фоне слабого иммунного ответа у этих больных. Кроме того, сравнительно легкое течение заболевания у пациентов с коинфекцией, вызванной ВИЧ/SARS-CoV-2, может быть связано с применением АРВТ. Несмотря на отсутствие протективного действия АРВТ в отношении заражения вирусом SARS-CoV-2, исследователи предполагают, что АРВТ может стабилизировать иммунный ответ у коинфицированных пациентов, что препятствует прогрессированию заболевания до тяжелых форм.

Ключевые слова: COVID-19, SARS-CoV-2, ВИЧ, вирус иммунодефицита человека, антиретровирусная терапия, ВИЧ/SARS-CoV-2-коинфекция, лица живущие с ВИЧ, ЛЖВ

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The coronavirus disease pandemic, announced by the World Health Organization in 2020, plays a central role in destabilizing health systems around the world, spreading rapidly and causing adverse outcomes. The SARS-CoV-2 high risk groups have been identified, yet pregnant women, children and chronic patients still constitute groups with "unclear" vulnerability, both socially and clinically, which is the reason for concern on the part of the medical community. Among the said groups, HIV patients form a separate category due to the immunodeficiency nature of the disease and its treatment peculiarities. Moreover, in many parts of the world it is difficult for HIV patients to get medical care, and with SARS-CoV-2 coinfection, their adherence to treatment protocols may become even more complicated. It is already known that the coronavirus infection manifestations in HIV patients were mainly limited to intestinal disorders, such as diarrhea, and rarely led to severe respiratory symptoms [1]. During the outbreak of SARS in 2003, only a few cases of the disease were registered in HIV-positive people, all of them mild [2]. In 2012, Middle East respiratory syndrome caused by MERS-CoV was a severe disease entailing high mortality, but it did not affect people living with HIV (PLHIV) significantly: the registered case describes patient's recovery [3]. The short duration of the aforementioned outbreaks has disallowed large-scale investigation of the ART's potential as the anticoronaviral therapy. Thus, it is important to clarify all the possible aspects of coinfection with two potentially dangerous viruses, their strength, interaction, the impact of ART and other issues.

Key features of COVID-19 and HIV infection

The first COVID-19 (Coronavirus Disease 2019) cases were registered in December 2019 in Wuhan (Hubei Province, China). The infectious agent was identified as a novel enveloped RNA beta coronavirus dubbed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). As of January 2021,

it caused a disease in over 93 million cases worldwide. While the susceptibility to COVID-19 seems to be high, the risk of severe COVID-19 course increases with age and peaks in those over 65. Studies have shown that men may be more susceptible to the infection than women, and the incidence in children is lower than in adults [4]. It was also established that concomitant diseases, including arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular and cerebrovascular diseases, increase the risk of COVID-19 infection and the associated complications [5, 6].

The main routes of transmission of the disease from person to person are droplet and contact, with the former involving respiratory droplets and the latter virus transfer from a contaminated surface to the mucous membrane of the host. In 70% of patients, the symptoms of COVID-19 never manifest or manifest lightly; in 30% of patients the virus causes fever and a respiratory syndrome that can develop into a severe respiratory failure requiring intensive care [7]. The infection also frequently manifests as cardiovascular, neurological and gastrointestinal disorders. The most widely used diagnostic method relies on PCR (polymerase chain reaction). It aims to detect the nucleic acid of SARS-CoV-2. Serological methods are used to detect antibodies to SARS-CoV-2 in plasma and whole blood [7]. The recently developed T-Detect Assay, a T-cell test, offers higher accuracy in determining a pastinfection than antibody serology assay, and therefore can be regarded as a sensitive and reliable method to establish if a person has been infected earlier. This test confirms the special role of T-cells in the development of immunity to SARS-CoV-2 [8].

The treatment for COVID-19 is largely symptomatic and supportive, focused on preventive strategies. The antiviral agents involved are remdesivir and favipiravir, which can suppress SARS-CoV-2, improve the patient's clinical status and shorten the recovery period [9, 10]. In addition, based on the previous experience with SARS and MERS and the results of *in vitro* studies, researchers have also tested ribavirin, interferon, chloroquine/hydroxychloroquine, lopinavir-ritonavir for the purpose, with the latter seemingly delivering slightly better results than the former. [11]. In severe cases, it is recommended to administer corticosteroids [12].

HIV, transmitted during unprotected sex, through blood when sharing non-sterile tools and transfusing contaminated blood products, and transmitted from an HIV-positive mother to her child, has caused millions of deaths worldwide and continues to spread among the population. Having entered the body, HIV replicates in activated T-cells, migrates to the lymph nodes, which leads to a decrease in the overall $CD4^+$-T-cell count and inversion of the $CD4^+/CD8^+$ T-cells ratio. As a result, the host's immune response grows weaker, making it susceptible to various opportunistic diseases, mainly viral and mycotic by nature. ART suppresses the viral load, which translates into lower HIV transmission risk, immune system restoration, prevention of secondary diseases, HIV patient's life duration and quality improvement.

From both diagnostic and clinical points of view, HIV/SARS-CoV-2 coinfection is a combination of two separate diseases, so considering their peculiarities is critical to understanding how they interact. The clinical picture of the disease and the treatment protocols developed for the HIV/SARS-CoV-2 patient group may differ from those for the general population, therefore, a thorough study of cases from this group can give us valuable information about the behavior of viruses within a single host, the peculiarities of disease progression, effective treatment strategies.

COVID-19 course and outcomes in HIV patients: cases and discussion

Up to the present, the number of PLHIV infected with SARS-CoV-2 has remained low. However, it is best to practice caution in interpreting this fact: it does not prove that HIV-positive people are less susceptible to contracting the disease, it may simply be the result of HIV patients taking more serious precautions to limit their exposure to SARS-CoV-2 [13].

One of the first cases of HIV/SARS-CoV-2 coinfection was reported in Wuhan. The patient was 61-year-old man, longtime smoker with type 2 diabetes and long dry cough and fever manifestations. His blood test showed he suffered from mild lymphopenia, which grew severe (lymphocyte count 0.56×10^9/L, relative $CD4^+$-T-lymphocyte count 4.75%). Treatment included lopinavir/ritonavir on admission, moxifloxacin, gamma globulin, and methylprednisolone. The patient recovered and was discharged in 20 days after the first visit to the clinic [14].

A population study conducted in Wuhan among HIV/SARS-CoV-2-coinfected people revealed no difference in the severity of the disease and mortality associated with COVID-19 in HIV patients and general population. It is reported that the incidence of COVID-19 among PLHIV on ART is 0.52%, 2.20% among PLHIV who have interrupted ART, and 0.63% among PLHIV who have never had ART [15].

Based on the few HIV/SARS-CoV-2 coinfection studies available to date (Table), the international medical community has concluded that HIV infection is not an independent risk factor affecting COVID-19 infection possibility and the severity of the disease [16]. PLHIV on ART, with suppressed HIV viral load and over 200 cells/μl of $CD4^+$-T-lymphocytes, endure COVID-19 comparably to the general population [13, 17, 19]. Same as in the general population, the severity of the disease in coinfected individuals depends on age, gender, and concomitant diseases such as diabetes and hypertension [18, 19]. One of the findings is that HIV/SARS-CoV-2 patients often have a greater number of comorbidities than people not suffering the diseases [18].

However, a number of researchers report opposite results. For example, a retrospective study of HIV/SARS-CoV-2 coinfection cases conducted in New York clinics showed that, compared to the HIV-negative cohort, HIV-positive patients were more likely to need intensive care, invasive mechanical ventilation (IMV), died or were discharged to a hospice more often. At admission, radiological examination results of HIV patients commonly presented various pathologies. Three HIV/SARS-CoV-2 patients had bacterial complications and died. All HIV-positive patients, except one, were on ART and had the $CD4^+$-T-lymphocyte count of over 200 cells/μl [20].

A large cohort study that involved 22,308 patients in South Africa also reported a two-fold COVID-19-associated death risk increase in HIV-positive persons. However, the author of this study did not exclude the effect of confounding, which may cast doubt on the results [21].

Some other factors considered in addition to comorbidities as potentially capable of influencing the outcome are poor immune status, race, ART regimen. The authors of one of the prospective cohort studies involving 51 patients with controlled HIV infection conclude that an unfavorable outcome (severe course of COVID-19 and death) is probably associated with a $CD4^+$-T-lymphocyte count of less than 200 cells/μL [22].

A case series published by the King's College Hospital (UK) describes clinical characteristics of 18 PLHIV (mean age 52 years) who were admitted with COVID-19. It was found that the majority of patients belong to the Negroid race, have

Table. Studies researching the impact of HIV on COVID-19 course

Authors	Year	Region	Number of patients	Design	Key results
Shalev N et al.	2020	USA	31	Transverse	COVID-19 course and outcome in PLHIV on ART with CD4 >200 comparable to those in general population
Gudipati S et al.	2020	USA	14	Transverse	COVID-19 course and outcome in PLHIV comparable to those in general population
Stoeckle K et al.	2020	USA	120	Longitudinal	COVID-19 course and outcome in PLHIV comparable to those in general population
Karmen-Tuohy S et al.	2020	USA	63	Longitudinal	COVID-19 course and outcome in PLHIV comparable to those in general population
Inciarte A et al.	2020	Spain	62	Longitudinal	COVID-19 course and outcome in PLHIV comparable to those in general population. PLHIV exhibit lower incidence than the general population
Vizcarra P et al.	2020	Spain	51	Longitudinal	The risk of a severe course of COVID-19 among PLHIV is not lower than in the general population
Davies MA	2020	Western Cape Province, South Africa	22308	Longitudinal	Doubled risk of death of PLHIV from COVID-19
Huang J et al.	2020	China	35	Longitudinal	COVID-19 course and prognosis in PLHIV may be more adverse compared to those in general population
Suwanwongse K et al.	2020	USA	9	Transverse	HIV infection and low immune status may negatively impact COVID-19 outcomes
Gervasoni C et al.	2020	Italy	47	Transverse	Reduced risk of severe course and adverse outcomes of COVID-19 in PLHIV

a lower median number of CD4$^+$-T-cells and tend to use more protease inhibitors in the ART regimen than outpatients [23].

According to a study conducted in Turkey, out of 1224 HIV-positive individuals only four male patients contracted SARS-CoV-2, and three of them had no underlying conditions and recovered fully. All three patients were on ART; COVID-19 in their cases was mild. The fourth patient, a 44-year-old man, was on ART, with low HIV viral load, high CD4$^+$-T-cell counts and several comorbidities. This patient died, proving that from the point of view of comorbidities, HIV-positive people have the same predictors of adverse disease outcome as general population [24].

A number of other researchers report similarities in how people with controlled HIV (as evidenced by high CD4$^+$-T-cells and low viral load) and the general population endure COVID-19. The authors conclude that the reported deaths are caused by old age and multiple comorbidities [25, 26].

There are results of the analysis of all admissions of PLHIV with SARS-CoV-2 coinfection that are worth mentioning: most patients were on ART for a long time, their HIV viral load was suppressed or minimal, and the count of CD4$^+$-T-lymphocytes exceeded 200 cells/μL. Only a few patients were not on ART, had a detectable HIV viral load and CD4$^+$-T-cell count below 200 cells/μL. These patients recovered quickly [25].

Researchers from Spain described 5 cases of coinfection and reported interesting observations: a patient not on ART and with CD4$^+$-T-lymphocytes counting less than 200 cells/μL needed non-invasive ventilation only and was discharged without any complications, while another patient with a CD4$^+$-T-lymphocyte count of more than 200 cells/μL and a suppressed HIV load needed invasive mechanical ventilation [18].

Similarly, a 28-year-old male coinfected with SARS-CoV-2 and HIV, without comorbidities, showed no severity in his disease progression and improved smoothly in 9 days, eventhough his immune status from HIV infection was not well-controlled (CD4$^+$-T-cell count is 194 cells) due to a lack of ART [27].

A similar trend was reported in another retrospective cohort study of 23 patients with HIV/SARS-CoV-2 coinfection. Three patients from the cohort were discharged home without complications, while for the patients with undetectable viral load and relatively high CD4$^+$-T-lymphocyte counts (over 400 cells/μl) the outcome was unfavorable. In this case series, CD4$^+$-T-cell lymphopenia was recognized as a factor protecting COVID-19 progression to severe stages, and the ART regimen was stated to have no effect on the outcome [28].

A single-center prospective study conducted in Italy tracked the outcomes of HIV/SARS-CoV-2 coinfection cases; this effort also revealed no association between immunosuppression and the disease progressing to its severe forms. It is reported that the only patient with severe COVID-19 was a Caucasian male whose immunological profile was optimal (baseline CD4$^+$-T-lymphocyte count of 438 cells/μL), while two Negroid patients with severe immunodeficiency and comorbidities had the disease asymptomatic [29].

In another retrospective study, the majority of the participants from the coinfection cohort had the viral load suppressed and the count of CD4$^+$-T-lymphocyte acceptable; these patients had several comorbidities and were on average 10 years younger than the HIV-negative cohort. It was shown that the risk of severe COVID-19, admission to intensive care unit and death was significantly lower in HIV-positive patients. However, it should be borne in mind that this study included HIV patients with COVID-19 not confirmed by laboratory methods, so its results may be questionable [30].

The reports published suggested that HIV-associated immunosuppression may paradoxically protect against severe manifestations of COVID-19 [17, 30, 31]. In one of the studies, the HIV group exhibited low peak CRP levels, which, according to the researchers, signals difficulties with development of a pronounced immune response. It would seem like the relative immune dysfunction plays a protective role in case of COVID-19 contraction, which makes the need for non-invasive and invasive mechanical ventilation experienced by PLHIV less urgent [19].

Recent reports have shown that HIV/SARS-CoV-2 coinfected patients who had a fatal outcome had higher levels of soluble markers of immune activation and inflammation than those who survived, suggesting that PLHIV remain capable of a profound inflammatory reaction in response to SARS-CoV-2 coinfection [13, 22, 32].

An inverse relationship was noted between the number of CD4+-T-lymphocytes and the mortality rate. A case series covering HIV/SARS-CoV-2 patients admitted to the South Bronx Hospital, New York, describes nine participants (seven male, two female), aged 58, with multiple comorbidities, CD4+-T-lymphocyte count of 179–1827 cells/μL and HIV viral load from very low to undetectable [33]. In the context of the series, the researchers concluded that the predictors of disease progression to its severe form and death are similar in HIV-positive and HIV-negative groups. Comparing their findings to the data reported in other studies, the authors state the patients they worked with had a significantly lower CD4+-T-lymphocyte count, but their mortality rate was higher, which allows refuting the protective effect of immunosuppression. The results of the study, however, must be interpreted with caution, as the majority of the involved patients seeing adverse outcomes were not on ART, had CD4+-T-lymphocyte counts greater than 200 cells/μL and suffered multiple comorbidities [33].

Along with the conflicting reports on the peculiarities of COVID-19 in HIV-positive individuals, it is necessary to consider another theory that holds the possible effects lopinavir/ritonavir has on SARS-CoV-2, the initiation time and ART regimen balancing the immune response and clearance of coronavirus, thus preventing the development of an unfavorable hyperinflammatory condition in coinfected patients [34].

We hypothesize that severely immunocompromised patients themselves are not protected from COVID-19, they only may have the disease asymptomatic or manifesting mild symptoms because they are unable to develop a sufficiently strong inflammatory response to aggravate the symptoms. Thus, such patients are admitted to hospitals less often. However, such immunosuppression cannot be called a protective factor, as it can lead to prolonged viral clearance. With the virus clearance delayed and depending on a number of factors (comorbidities, patient age, timeliness of treatment, ART regimen etc), asymptomatic COVID-19 can progress to its mild to severe forms, sometimes leading to death.

A large-scale testing of HIV-positive individuals for antibodies (outpatients) could help clarify whether all immunosuppressed COVID-19 patients indeed have asymptomatic form of the disease [31].

At the same time, most of the HIV/SARS-CoV-2 patients involved in the studies had a CD4+-T-lymphocyte level in excess of 200 cells/μL, which, we assume, could add symptoms to the course of the disease. In this group of patients, COVID-19-induced lymphopenia was superimposed on the existing mild or moderate immunosuppression, which probably caused a stronger response against the background of previously prescribed ART, thus increasing the number of lymphocytes to the level of a stabilized immune response that prevents serious inflammation- or virus-caused damage.

There is another theory, which has the milder course of the disease a result of action of the viral interference mechanism, when HIV changes the host cells and creates the environment unfavorable for other viruses, thus modifying the course of COVID-19.

Immunological characteristics of HIV/SARS-CoV-2 patients

Transient lymphopenia is common against the background of COVID-19, but when combined with progressive HIV-associated lymphopenia, lymphocyte counts in HIV/SARS-CoV-2 coinfected patients improve only marginally after recovering from COVID-19 [35].

The relatively lower number of CD4+-T-lymphocytes in HIV/SARS-CoV-2 patients may be one of the reasons behind the blurred clinical picture, as well as delayed and insufficient production of antibodies to SARS-CoV-2. Moreover, the low levels of IgM and IgG to SARS-CoV-2 were associated with a higher HIV viral load, i. e. ≥ 20 copies/ml, as compared to patients with a viralload below 20 copies/ml [15].

A retrospective study of COVID-19 in PLHIV revealed severe lymphopenia and a decrease in the number of CD4+-T-lymphocytes, while the levels of CRP, fibrinogen, D-dimer, interleukin-6, interleukin-8 and TNFα were increased. Higher levels of inflammatory markers and more severe lymphopenia were reported in HIV patients for whom COVID-19 ended adversely compared to those who recovered [36]. While in general population higher interleukin-6 and d-dimer levels are associated with the severity of COVID-19, in PLHIV they may be interpreted as biomarkers of chronic HIV infection [37]. Nevertheless, there were no biomarker content differences registered between HIV/SARS-CoV-2 patients and HIV-negative COVID-19 patients.

Severe lymphopenia can be explained by the accelerated apoptosis of lymphocytes against the background of a viral infection that activates them in the context of antiviral response [38]. Another explanation for lymphopenia may be the direct effect SARS-CoV-2 produces on lymphocytes through ACE2-dependent and ACE2-independent pathways. It was reported earlier that less than 5% of oral mucosa lymphocytes can express ACE2 [39]. Besides, SARS-CoV-2 can use CD147 receptors to enter T-cells [40].

COVID-19 and antiretroviral therapy

Patients with ART-controlled HIV infection run roughly the same risk of contracting COVID-19 as the general population [14], however, the effect ART has on HIV/SARS-CoV-2 coinfection remains to be studied further. The main reason why earlier studies hypothesized about the protective effect of ART against COVID-19 in PLHIV was that antiviral drugs, such as tenofovir and lopinavir, showed anti-SARS-CoV-2 activity in vitro [41, 42]. This is indirectly confirmed by the results of a retrospective study that included 20 HIV/SARS-CoV-2 patients and reported lower ESR and CRP in those on ART compared to the patients who did not receive such therapy [43].

A clinical trial involving hospitalized adult HIV-negative patients with confirmed novel coronavirus infection showed no significant difference in the timing of clinical improvement backed by lopinavir/ritonavir treatment. However, the mortality rates at 28 days, the time in ICU/hospital registered by the researchers were generally lower, and more patients showed clinical improvement on day 14 in the lopinavir/ritonavir group compared to the standard treatment group. Compared to the standard supportive regimens, protocols including lopinavir/ritonavir enable reduction of SARS-CoV-2 RNA load and shorten the time when viral RNA remains detectable [44]. Despite the reported results suggesting the potential clinical benefits of lopinavir, it is necessary to evaluate the effectiveness of this drug in HIV/SARS-CoV-2 patients [34].

Another HIV/SARS-CoV-2 case series report describes the ART prescribed to the majority of patients and including of a protease inhibitor, predominantly darunavir, boosted with ritonavir or cobicistat [23].

It has also been reported that 800 mg darunavir has no protective effect against infection and progression of respiratory failure, while for the patients that mainly received integrase inhibitors COVID-19 ended favorably [30].

Spanish researchers have shown a higher prevalence of SARS-CoV-2 among those who resorted to pre-exposure prophylaxis regimen of tenofovir disoproxil fumarate or tenofovir alafenamide and emtricitabine (TDF/TAF+FTC); compared to the control group, they exhibited no significant differences in clinical manifestations [45], which refutes the hypothesis about the protective effect of tenofovir against SARS-CoV-2 [42]. Several other studies also report a higher proportion of HIV/SARS-CoV-2 patients on TDF-based ART compared to patients with HIV alone [17, 22].

More research is needed on nelfinavir mesylate, an HIV protease inhibitor that has recently been found to be an effective inhibitor of the SARS-CoV-2 S-protein, the main determinant of viral infectivity [46].

Conclusion

It is likely that in HIV-positive patients on virologically and immunologically effective ART, the course of COVID-19 is comparable to that in general population. Apparently, ART does not reduce the risk of SARS-CoV-2 infection, however, stabilization of the immune system during therapy can help reduce the incidence of adverse COVID-19 outcomes. SARS-CoV-2-associated lymphopenia superimposed on immunodeficiency can make the clinical picture blurred, delay virus clearance and production of antibodies to SARS-CoV-2 and make their count insufficient. It is unclear whether SARS-CoV-2-associated lymphopenia facilitates development of opportunistic diseases or not. The above is a powerful argument for taking all precautions in HIV-positive patients.

The available information on HIV/SARS-CoV-2 coinfection appears to be rather controversial and has many gaps. This reasons behind the situation being as it is may be associated with an insufficient sample size of HIV/SARS-CoV-2 patients in some studies, lack of a large-scale effort to diagnose asymptomatic cases, underestimation of the predisposing factors when comparing HIV/SARS-CoV-2 patients with people hosting HIV only, which leads to faulty estimation of the effects of confounding of comorbid conditions, ART regimen on the development of an adverse outcome in coinfection cases. Subsequently, the results of the study are distorted. Thus, more research is needed to confirm or refute some of the proposed hypotheses, as well as to assess the effectiveness of ART in HIV/SARS-CoV-2 coinfection cases.

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