ORIGINAL ARTICLE

SARS-CoV-2 infection in adults and HIV: an update

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ABSTRACT

Aim COVID-19 pandemic caused by SARS-CoV-2 is spreading throughout the world affecting both healthy individuals and people with underlying immune-deficiencies. People living with human immunodeficiency virus (HIV) consist a group multiply affected by this universal crisis.

Methods Literature search aiming to identify relevant publications referring to the consequences of the COVID-19 pandemic in HIV infected population.

Results A body of literature is rapidly growing in regard to epidemiological data, the interaction between HIV and SARS-CoV-2, and clinical outcome in people living with HIV. Intensive research is warranted to identify any interactions of the co-existence of the two viruses in the immune system of HIV infected patients as common pathophysiology and molecular aspects are recognized. Human relations are diminished as a result of the social measures, and detailed recording of the consequences in this population is needed.

Conclusion Further research could shed light on the common underlying molecular mechanisms of both conditions in an attempt to discover treatment regimens for SARS-CoV-2 infection.

Key words: AIDS, COVID-19, pandemic

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Original submission:
09 October 2021;
Revised submission:
16 November 2021;
Accepted:
10 December 2021
doi: 10.17392/1440-21

Med Glas (Zenica) 2022; 19(1): 32-40

INTRODUCTION

In December 2019 the first case of a respiratory tract infection due to the novel SARS-CoV-2 was reported in the city of Wuhan, China (1). Ever since this novel virus that is classified as a member of the Corona *viridae* family (2) has spread all over the world causing a pandemic that has affected approximately 62 million patients and resulting at the time of this writing in almost 5 million deaths according to the World Health Organization (1). SARS- CoV-2 pandemic has been considered, especially due to many asymptomatic hosts and its high transmissibility, a major cause of mortality, especially for older people, those with severe comorbidities or a compromised immune system (3). However, the SARS- CoV 2 pandemic is not the last one that the mankind has experienced, the infection caused by the human immunodeficiency virus (HIV) is still ongoing with devastating consequences. Because of the fact that HIV targets directly CD4 (+) lymphocytes, the infected hosts experience a significant reduction of their immune system function (2). The treatment and follow-up of these patients, who would be of higher risk of a severe disease and death due to a potential SARS-CoV2 infection, have been a challenge for health systems all around the globe (4).

The aim of this research was to summarize the existing literature regarding clinical features and outcome of people living with HIV (PLWH) who had been infected with SARS-CoV-2. Furthermore, the aim was to highlight the existing common clinical and pathophysiological features of both viruses and discuss the way the current SARS-CoV-2 pandemic has affected the management and follow-up of PLWH.

MATERIALS AND METHODS

Materials and study design

We conducted a literature search aiming to identify relevant publications referring to the consequences of the COVID-19 pandemic in HIV infected population: HIV and SARS-CoV-2 co-infection, epidemiology and clinical outcomes, common pathophysiology and molecular aspects, effects of the SARS- CoV-2 pandemic on the management of PLWH, the role of antiretroviral therapy (ART) in Covid-19 treatment, and SARS-CoV-2 vaccine and PLWH.

Methods

A PubMed/Medline search was conducted aiming to identify all relevant publications when the terms “COVID-19 and HIV”, “COVID and AIDS”, “SARS-CoV-2 and HIV” and “COVID-19 and HIV review” from December 2019 to March 2021 were used. All types of publications were enrolled, also additional references were searched for related studies and only English written articles were finally enrolled.

RESULTS

The vast majority of PLWH reportedly infected with SARS-CoV-2 in the searched registries, ranging from 50% to approximately 80%, were males. In addition to this, the majority of PLWH reaching the emergency room (ER) because of SARS-CoV-2 infection was admitted for further intra-hospital management (from about 50% to 70%). Most PLWH were reported to have comorbidities related to metabolic syndrome, cardiovascular disease and chronic obstructive pulmonary disease (COPD).

Little evidence has been published about pre-existing co-infection with hepatitis B virus (HBV), hepatitis B virus (HCV), or tuberculosis (TB). According to the searched publications, in about 3 out of 4 patients in average the main complaint was related to symptoms of a respiratory infection (fever, cough, dyspnoea and/or documented infiltration in chest x-rays or CT scans). Loss of taste and smell was observed only in very few patients.

Overall, about 90% of the patients in average clinically improved and were therefore released, and intensive care unit (ICU) admission was required in approximately 10% of patients. A death rate was less than 10% in all researched publications (Table 1).

DISCUSSION

HIV and SARS-CoV-2 co-infection: epidemiology and clinical outcomes

Our results showed that a few hundred cases (approximately 400) of PLWH infected with SARS-CoV-2 have been reported worldwide (5–7)Scopus, and Web of Science for case reports and case series about COVID-19 in HIV patients. We finally reviewed 20 case reports

Table 1. Co-morbidities and clinical outcomes of people leaving with human immunodeficiency virus infected with COVID-19

Publication	No. of patients (males/females) (mean age in years)	Co-morbidities (No. or % of patients)	Clinical features (No. of patients)	Clinical outcome (No. / % of patients)
Geravsoni et al., 2020	47 (36/ 11) (51)	Hyperlipidaemia (15), HT (14), HBV/HCV co-infection (5), DM (2), CVD (2), COPD (2), cancer (3), CKD (4), epilepsy (2), organ transplant (1)	Fever (41), cough (23), dyspnoea (10), diarrhoea (10), myalgia (3), headache (2)	Hospitalization 13 (need for oxygen supply mechanical ventilation 6/13), fully recovered 45
Harter et al., 2020	33 (30/3) (48) 3	HT (10), COPD (6), DM (6), CVD (3), CKD (2), HBV/HCV co-infection (6)	Cough (25), fever (22), headache (7), anosmia (6), arthralgia/myalgia (7)	Hospitalization (14), ICU admission (6), deaths (3), fully recovered (30)
Del Amo et al., 2020	236 (204/32)	No data available	No data available	Hospitalization (151), ICU admission (15), death (20), fully recovered (216)
Dandachi et al., 2020	286 (212/74), (51.4)	HT (46.5), obesity (32.3), DM (21.3), overall co-morbidities existing at 80.3% of patient sample	Cough (205), fever (198), fatigue (140) abnormal CXR findings (150), abnormal chest CT scan findings (38)	Hospital admission (164), ICU admission (47), deaths (27), deaths in ICU (24)
Hsien Ho et al., 2020	93 (58)	Autoimmune conditions (4), cancer (8), DM (32), CVD (17), HT (49), CKD (23), organ transplantation (5)	Anosmia (2), diarrhoea (18), headache (17), fever (61), hypotension (5), cough (71), hypoxia (SO2< 92%) (43), myalgia (33), dyspnoea (33), nose congestion (13), sore throat (13), altered mental status (13)	Release directly from ER (21), hospital admission (72), ICU admission (19)
Stoeckle et al., 2020	30 (60.5)	HT (2), DM (8), CVD (2), COPD (4), asthma (3), CKD (2), heart failure (1), HBV/ HCV co-infection (7)	Cough (21), dyspnoea (20), diarrhoea (10), headache (3), myalgia (4), fever (17), anosmia (1), loss of taste (2), nausea/ vomiting (5), chest pain (3)	No data published
Morani et al., 2020	43 (51.56)	CVD / COPD (25), DM (9), atrial fibrillation (3), hypertensive nephropathy (14)	Fever (32/43), cough (29/43), diarrhoea (9/43), headache (8/43), dyspnoea (16), hypoxia (2), tachycardia (11), fatigue (5), vomiting (2), myalgia (5), anosmia (1), loss of taste (1)	Recovered (37), death (6)
Cabello et al., 2020	63 (88.9% males)	HT (19), CVD (19.7), DM (9.5), obesity (13), smokers, ex- smokers	Fever (66.5), cough (66.1), dyspnoea (46.8)	Hospital admission (1/3), ICU admission 3.17%, overall death rate 3.17%

HT, hypertension; HBV/HCV, hepatitis B/C; CVD, cardiovascular disease; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ICU, intensive care unit; CXR, chest X- ray; ER, emergency room;

including cases of 43 patients with HIV and COVID-19. The mean age of 43 adult patients was 51.56 ± 27.56 years (range 24–76 years. This figure might not be indicative of the actual spread of SARS-CoV-2 among PLWH, given the fact that, according to the latest estimates, almost 39 million people have been infected with HIV (8,9) with devastating effects on individuals, communities, and societies across the world. People with chronic health conditions may be at greater risk of contracting or experiencing complications from COVID-19. In addition to illness or death for those who contract the virus, the physical distancing required to flatten the curve of new cases is having a negative impact on the economy, the effects of which intersect with mental health and other existing health concerns, thus affecting marginalized communities. Given that HIV also has a disproportionate impact on marginalized communities, COVID-19 is affecting people with HIV (PWH, and the majority of published cases comes mostly from developed countries (10,13,such as people living with HIV/AIDS (PLWHA14) and not from the areas that have been severely hit by the HIV pandemic, in particular from sub-Saharan countries (5–7, 10,15) such as people living with HIV/AIDS (PLWHA.

Initially it was hypothesized that PLWH might have better clinical outcomes compared to non–HIV infected people, based on the assumption that due to the damage on cellular immunity the patients would probably not experience the immune over-activation (16) that leads to uncontrolled release of cytokines, that is the main cause of acute respiratory distress syndrome (ARDS) and/or organ dysfunction in critically ill SARS-CoV-2 patients (17). However, the existing clinical data have shown quite a different effect.

Overall possibility of being infected with SARS-CoV-2 has not been significantly different between PLWH and the patients suffering from other diseases (5,6,18). In detail, studies coming from Europe and the USA suggest that PLWH are not at greater risk of being infected with SARS-CoV-2 (19,20) or having more severe clinical features, although a large study from South Africa suggests that the possibility of contracting SARS-CoV-2 could be slightly greater for PLWH in comparison to other people. Similarly, to the non-HIV infected patients, age, male sex and the existence of comorbidities are associated with an increased risk of more severe clinical manifestations and death. In particular, among PLWH an increased incidence of mortality due to cardiovascular disease has been noticed (5). Interestingly, PLWH infected with SARS-CoV-2 experienced overall less sense of dyspnoea and did not experience lower oxygen saturation measured with pulse oximetry (5,6). Moreover, as it has been noticed in immune compromised patients (21), mortality of PLWH infected with SARS-CoV-2 is higher compared to the non-HIV infected patients with SARS-CoV-2 (13,22,23). A co-infection with SARS-CoV-2 led to further reduction of the CD4 (+) cell count, probably due to synergistic activity of both viruses (5,24,25), also on some occasions an increase in the appearance of the "exhausted lymphocytes" phenomenon has been observed. Both situations are considered to be negative prognostic factors associated with worst clinical outcome (26).

SARS-CoV-2 can be transmitted from one host mainly through droplets originating from the upper and/or lower respiratory system in order to infect other people (27,28); airborne transmission is also considered as a possible way of SARS-CoV-2 transmission on some occasions (27). On the other hand, HIV is known to be transmitted either through sexual contact, injury by infected sharp objects such as needles and/or through contact with infected blood (29). The latter appears to be the main reason why HIV can be transmitted vertically, from mother to foetus (28–30). However, SARS-CoV-2 has proven also to be vertically transmitted from mother to foetus/newborn child on a few occasions (31). The existing literature does not provide any explanation about the causes and/or the underlying mechanism. It has been reported that SARS-CoV-2 has been detected in blood samples from infected patients, and that viremia in SARS-CoV-2 infection is associated with a worse clinical outcome overall (32). However, no blood-borne SARS-CoV-2 infection has ever been reported after transfusion of blood from initially asymptomatic SARS-CoV-2 patients to other patients (33,34). Since the testing of donated blood for SARS-CoV-2 RNA is not suggested by the existing guidelines (33,35), it is unclear if SARS-CoV-2 can be transmitted through infected blood like HIV, because so far only a few such cases have been published (36).

An increased viral load of HIV and not taking any anti-retroviral medication are considered negative factors regarding the clinical outcome of PLWH suffering from SARS-COV2 infection (6). Furthermore, a decrease in CD4 (+) cell count was associated with worse clinical course of the SARS-CoV-2 co-infection (5,6,37,38)Scopus, Web of Science, Embase, preprint databases, and Google Scholar from December 01, 2019, to June 1, 2020. From an initial 547 publications and 75 reports, 25 studies provided specific information on COVID-19 patients living with HIV. Studies described 252 patients, 80.9% were male, the mean age was 52.7 years, and 98% were on antiretroviral treatment (ART. PLWH receiving antiretroviral treatment (ART), and in particular tenofovir and emtricitabine had better clinical outcomes and the need for hospital admission was lower compared to PLWH receiving other kinds of treatment (39).

HIV and SARS-CoV-2 co-infection: common pathophysiology and molecular aspects

In both HIV and SARS-CoV-2 infections a sudden and extreme rise in the serum concentration of inflammatory cytokines, known as "cytokine storm", has been observed (40,41). On both occasions cytokine storm is associated with more severe clinical features (23,40), and particularly in COVID-19 it is considered the main factor that causes ARDS and multi-organ failure, leading to increased mortality (23,41). Some studies propose the IL-6 as the main inducer (or amplifier) of the cytokine storm. The chemokine receptor CCR5, which has been studied extensively during the AIDS pandemic because it functions as the receptor – gateway to HIV in its host cell, appears to have also a critical role in inducing cytokine storm; it could possibly be a therapeutic target for SARS-CoV-2 infection as well (17).

Its main action is by reducing the impact or even prevent the initiation of a cytokine storm. In this context the knowledge about the structure and the polymorphism of the gene of CCR5 that has been acquired during HIV research could be of great value for COVID-19 as well (42,43)which, in turn, influences HIV infection acquisition and subsequent disease progression. Among these polymorphisms, a 32-bp deletion in the CCR5 open reading frame (CCR5 Δ32.

HIV targets lymph cells and in particular CD4 (+) cells, resulting in reduction in the overall lymph cell count (lymphopenia) and an impaired function of the entire immune system. Decreased number of lymphocytes has also been reported in SARS-CoV-2 infection (44) and it is associated with a more severe clinical outcome. In SARS-CoV-2 infection CD8(+) cells are particularly reduced and their increase is considered as an indication of clinical improvement (45,46). The exact mechanism under which SARS-CoV-2 causes lymphopenia is still under investigation. On many occasions lymph cell exhaustion has been observed after the prolonged overexposure of lymph cells to the increased concentrations of inflammatory cytokines in serum, leading to the detection of cell – death markers in the surface of lymph cells. Furthermore, it has also been hypothesized that SARS-CoV-2 could directly enter lymph cells and induce their destruction or that could also infiltrate and have a toxic effect in lymph nodes and the spleen (26,44). Overall, it is estimated that HIV and SARS-CoV-2 might act synergistically and further reduce the number of lymph cells.

Both infections of HIV and SARS-CoV-2 are characterized by an increased incidence of thrombus formation, resulting in the creation of thrombotic emboli that need further anticoagulation treatment and/or prophylaxis (47,48). The creation of thrombus emboli is often associated with the number of CD4 (+) cells, and the risk of thrombosis increases as the CD 4 (+) cell count decreases (49,50)and to assess the correlation of thrombosis with the degree of immunosuppression as well as the association with active illnesses and neoplasms, we reviewed the charts of 131 patients, which include all the patients with the diagnosis of HIV admitted or seen in the clinic between January 1, 1993, and January 1, 1998. The diagnosis of thrombosis was based on documented reports of venous plethysmography or venography for deep venous thrombosis and ventilation-perfusion scan or pulmonary angiography for pulmonary embolus. Risk factors for thrombotic disease were evaluated including general risk factors such as family history, ambulatory status, medications, and data were also collected regarding CD4 cell counts and the presence of concurrent or remote opportunistic infections, acquired immune deficiency syndrome (AIDS. Their creation is caused by a multitude of factors, since multiple defects in the innate anti- thrombotic system have been detected, most notably the circulation of auto-antibodies such as anti-phospholipid antibodies and dysfunction in the formation of thrombin (51). Although in COVID-19 autoantibodies have been detected (52), the main reason for increased clot formation appears to be the tissue factor up regulation (53)venous thromboembolic disease, and stroke. Importantly, thrombotic complications are markers of severe COVID-19 and are associated with multiorgan failure and increased mortality. The evidence to date supports the concept that the thrombotic manifestations of severe COVID-19 are due to the ability of SARS-CoV-2 to invade endothelial cells via ACE-2 (angiotensin-converting enzyme 2, similarly to HIV infection, as a result of the over-production and release of inflammatory cytokines and the subsequent endothelial cell damage and activation. All of the above appears to lead to the formation of thrombus emboli resulting in obstruction phenomena in the microvascular and the capillary network of the lung as part of the ARDS pathophysiology in COVID-19 (26,47). Up to date no data regarding the incidence of thrombosis specifically in SARS-CoV-2 infection in PLWH have been published although in literature similarities regarding common pathways of pathogenesis of thrombosis in both HIV and SARS-CoV-2 infections have been described (53)venous thromboembolic disease, and stroke. Importantly, thrombotic complications are markers of severe COVID-19 and are associated with multiorgan failure and increased mortality. The evidence to date supports the concept that the thrombotic manifestations of severe COVID-19 are due to the ability of SARS-CoV-2 to invade endothelial cells via ACE-2 (angiotensin-converting enzyme 2.

Effects of the SARS-CoV-2 pandemic on the management of people living with HIV(PLWH)

Since its first appearance in China SARS-CoV-2 has caused a crisis that has affected the management of people with chronic diseases. Based on data coming from the United Kingdom and China (8,9with devastating effects on individuals, communities, and societies across the world. People with chronic health conditions may be at greater risk of contracting or experiencing complications from COVID-19. In addition to illness or death for those who contract the virus, the physical distancing required to flatten the curve of new cases is having a negative impact on the economy, the effects of which intersect with mental health and other existing health concerns, thus affecting marginalized communities. Given that HIV also has a disproportionate impact on marginalized communities, COVID-19 is affecting people with HIV (PWH,54), PLWH have experienced restricted access to lab testing as part of their follow up, to obtaining their necessary antiretroviral treatment, also the initiation of ART has been delayed on many occasions (8,9,54)with devastating effects on individuals, communities, and societies across the world. People with chronic health conditions may be at greater risk of contracting or experiencing complications from COVID-19. In addition to illness or death for those who contract the virus, the physical distancing required to flatten the curve of new cases is having a negative impact on the economy, the effects of which intersect with mental health and other existing health concerns, thus affecting marginalized communities. Given that HIV also has a disproportionate impact on marginalized communities, COVID-19 is affecting people with HIV (PWH. The imposition of lockdowns and social distancing have worsened this situation by further discouraging PLWH to comply with their follow-up. Delays or postponement of follow-up and/or receiving and/or initiating the ART have been associated with an increase in HIV relapse and an overall clinical deterioration (9,54,55). Furthermore, according to prognostic models that have included data from African countries (15,25South Africa. We used Cox-proportional hazards models adjusted for age, sex, location and comorbidities to examine the association between HIV and COVID-19 death among (i,55), it is expected that new HIV infections might increase in the foreseeable future not only because the access to medical care and treatment has become more difficult during the culminating SARS-CoV-2 pandemic, but also because during the lockdowns the number of sexual contacts without protections has increased and the number of people seeking post-exposure prophylaxis has at the same time decreased (54,56).

The role of antiretroviral treatment (ART) in COVID-19 treatment

Medications used for the treatment of HIV infection have been evaluated as potential treatment against SARS-CoV-2infection (57,58). The concept of using such medications as a potential therapeutic approach against corona viruses is not new; it was also suggested during the SARS and MERS epidemic (59)recent cohort studies do not indicate this. Antiretrovirals(ARVs. During the current pandemic the observation that PLWH under ART have better clinical outcomes in some studies, even compared to non-HIV infected patients (60), has further encouraged investigators into the treatment of SARS-CoV-2 infection.

Both lopinavir/ritonavir inhibit the HIV- protease, preventing HIV from entering the host cell. Both were tested regarding their ability to inhibit the RNA- dependent RNA polymerase that SARS-CoV-2 uses in order to replicate its genome (61). Although there have been some promising *in vitro* results regarding the inhibitory effect of their combination (62), multiple studies suggest that their use does not provide any beneficial effect beyond standard care and therefore they are not indicated either for preventing or treating SARS-CoV-2 infection (63).

Tenofovir acts as an inhibitor of the reverse transcriptase. According to the latest studies it may be helpful as treatment and/or prophylaxis against SARS-CoV-2 (5,11,64)China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2. *In vitro* studies have shown that tenofovir is effective in inhibiting the SARS-CoV-2 RNA-dependent RNA polymerase (65)Chinese health agencies reported an outbreak of a novel coronavirus-2 (CoV-2 and in increasing the levels of IL-10 and IL-12, something that might contribute to a more effective response of the immune system against SARS-CoV-2, with increased levels of IFN-γand IgG against the virus in serum.

Emtricitabine is a cytosine nucleoside analogue that inhibits HIV's reverse transcriptase. PLWH under treatment with emtricitabine combined with tenofovir had overall better clinical outcomes in comparison to PLWH under no/other treatment regimen. Its role as a prophylactic agent against SARS-CoV-2 is under investigation in various ongoing clinical trials (59)recent cohort studies do not indicate this. Antiretrovirals(ARVs.

Little evidence exists for other ART agents (atazanavir, darunavir, cobicistat, saquinavir, integrase strand transfer inhibitors) regarding their use in COVID-19 management (59)recent cohort studies do not indicate this. Antiretrovirals(ARVs.

SARS-CoV-2 vaccine and people living with HIV (PLWH)

The latest development regarding the management of the SARS-CoV-2 pandemic, the mRNA-based vaccines are not contraindicated for PLWH according to the CDC (66) and the British HIV Association (67), although there are limited data regarding their efficacy in PLWH. A limited number of PLWH has participated in clinical trials for the development of both major mRNA vaccines, and although the findings related to them have not been included in the final official publication of the trials' outcome, no major risk issues emerged regarding PLWH receiving any vaccine (68,69).

A question is raised whether knowledge gained from the HIV- pandemic management could contribute to the management of the SARS-CoV-2 outbreak. Since both conditions are contagious and some kind of distancing, either sexual or social, is necessary for getting control of the further spread of each pathogen, behavioural measures and strategies that have been used in preventing the spread of HIV could be applied to the current pandemic of COVID-19 as well. As no specific medication treatment for SARS-CoV-2 infection has been identified yet, intensive research based on possible common mechanisms of action of the two viruses is warranted.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

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