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People living with HIV infection and SARS-CoV-2: What do we really know? SARS-Cov-2 infection in HIV patients

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Abstract

Since December 2019, the world healthcare community faced Coronavirus Disease 2019 (COVID-19) caused by a novel coronavirus (SARS-CoV-2). Due to the high viral contagiousness and the possible transmission during the pre-symptomatic phase, SARS-CoV-2 progressively spread to several countries. The worldwide outbreak of SARS-CoV-2 infection raised concern that people living with HIV infection (PLHIV) may be at high risk of infection and developing severe clinical manifestations. Currently, PLHIV patients could be considered particularly vulnerable to COVID-19 due to their immune-compromised status and their susceptibility to even opportunist pathogens. However, little is known about the impact of SARS-CoV-2 in PLHIV, particularly about pathogenesis and clinical outcomes, because, to the best of our knowledge, only case reports or small case series have so far been published.

The aim of this narrative review, based on a retrospective analysis of literature data, was to describe the epidemiological, clinical characteristics, diagnostic and therapeutical aspects, and possible outcomes of PLHIV with SARS-CoV-2 infection.

Despite the lack of specific studies, PLHIV should not be considered protected from SARS-CoV-2 infection or as having a lower risk of severe disease. Indeed, it is unclear if those with low CD4 cell counts, such as naïve HIV-patients, might have worse outcomes than individuals with restored immunity. Moreover, the clinicians should pay attention to uncommon clinical onset, manifestation and diagnosis in this cluster of patients. Because neither drug can be considered the first-line choice for treating SARS-CoV-2 infection, PLHIV should receive the same treatment approach as the general population.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is currently associated with a global pandemic causing Coronavirus disease 2019 (COVID-19), first identified in December 2019 in Wuhan, province of China. The virus was transmitted from human to human at an astonishing speed to many countries in the world. The spectrum of COVID-19 has ranged from a mild, self-limiting respiratory tract illness to severe progressive pneumonia, until acute respiratory disease, multi-organ failure, and death. It remains unknown what host factors may affect the clinical presentation of COVID-19. The severe forms of the illness predominantly occur in older adults (> 60 years) or with underlying comorbidities (hypertension, diabetes, cardiovascular disease, lung disease, and chronic kidney disease) and could be correlated with a worse prognosis.

According to currently limited information and clinical expertise, people with immunocompromised status, including anti-cancer treatment, organ transplantation, immune weakening conditions, and poorly controlled Acquired Immunodeficiency Disease Syndrome (AIDS), might be associated with increased risk of severe disease and death in patients with COVID-19 [1]. A systematic review with meta-analysis, analysing various causes of immunosuppression and immunodeficiency, concluded that they increased the risk of the severe clinical course of COVID-19 without a significant statistical difference [2].

The aim of this narrative review, based on the retrospective analysis of literature, was to describe the epidemiological and clinical characteristics, therapeutical aspects and possible outcomes of Human Immunodeficiency Virus (HIV)-infected patients with the diagnosis of SARS-CoV-2 infection.

Prevalence and case reports of SARS-CoV-2 infection in people living with HIV

No study reported the proportion of patients with COVID-19 tested for HIV infection, so It is impossible to evaluate the incidence of coinfection between COVID-19 and HIV. Without universal HIV testing, it is impossible to calculate the real incidence of coinfection of HIV and SARS-CoV-2 [3].

As reported by the Joint United Nations Programme on HIV/AIDS (UNAIDS), approximately 37.9 million PLHIV worldwide are at risk of COVID-19 [4]. Because of antiretroviral therapy (ART) and prevention policies, the number of PLHIV over the age of 50 years

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has increased dramatically, and it is estimated that more than 1/5 of PLHIV globally are in this older age group [5]. Also, PLHIV have a higher risk of comorbidity than the general population because of chronic inflammation and immune activation from HIV, ART side effects, and traditional risk factors such as alcohol and tobacco use [6]. The prevalence of SARS-CoV-2 infection in HIV-population is similar in various published cohorts, about 1%.

Blanco et al. reported the first single-centre experience of COVID-19 in patients infected with HIV-1 [7]. Two weeks into the COVID-19 outbreak in Spain, 543 consecutive patients with SARS-CoV-2 infection were admitted, and five of them (0·92%; 95% CI 0·39-2·14) were HIV positive. Mirò et al. [8] reported that 42 HIV-infected patients with COVID-19 visited the hospital clinic emergency department, 32 (76%) out of 42 subjects were admitted, and only one new case of HIV was diagnosed among them. These groups represent 0.7% of the 5649 patients in the institution's HIV cohort, 1.9% of the 2215 emergency department visits, and 1.5% of the 2102 hospital clinic admissions. A prospective observational study conducted in Madrid included all consecutive HIV-infected individuals with suspected or confirmed COVID-19 as of 30th April 2020 [9]. The incidence rate in HIV-infected individuals was 1.2 % for established confirmed COVID-19 and 1.8% for included suspected.

The prevalence of HIV-infected patients with COVID-19 was, therefore, similar to the findings of a Chinese survey [10] reporting 0.7% of HIV-infected cases with COVID-19 (eight out of 1174), whereas the rate of HIV hospital admissions was slightly higher than the 0.8% (42 of 5700) reported in New York City [11]. Sigel et al. [12] describe a cohort of 88 PLHIV with laboratory-confirmed COVID-19 admitted in five hospitals in New York City between March and April 2020. This PLWHIV - cohort was compared to an HIV-uninfected cohort of 405 patients affected by COVID-19 (matching 1 PLHIV to up to 5 patients). The authors did not find a significant difference in intensive care admission for HIV – cohort, and poor outcomes were similar in the two cohorts. Thus they conclude that HIV was not significantly associated with death risk, and no differences were found in adverse outcomes associated with HIV infection for hospitalised COVID-19 patients compared with a similar not HIV group.

Another large HIV cohort in New York City was described by Hsi-en Ho et al. [13]. They collected and analysed all PLHIV data with COVID-19 presenting to 5 New York City emergency departments between 2nd March 2020 and 15th April 2020. The high prevalence of comorbidities and the severity of COVID-19 were similar to reports in people without HIV. As the literature suggests, mortality in COVID-19 was associated with more severe lymphopenia, and it may predict COVID-19 severity. All these featuring are confirmed for the general population and PLHIV. In this study, the fatality rate among PLHIV affected by COVID-19 was higher than reported in the literature, and it was similar to that described in transplant recipients and those on treatment by immunomodulatory agents [14,15].

Probably, these reports underestimate the extent of the virus's spread in PLHIV because of the low number of completed SARS-CoV-2 tests and inadequate case reporting across the different areas of the world. According to the published cases of coinfection HIV/SARS-CoV-2 until 23rd March 2021, we resumed the founded clinical reported cases in table 1, and below, we described the most significant and peculiar aspects of some of them.

Peculiar aspects of pathogenesis

Understanding the physiological and immunological processes underlying the clinical manifestations of COVID-19 could explain possible risk factors, like immunosuppression, and it is essential for the identification and rational design of effective therapy. The human immune system is involved in the pathological process of COVID-19. Both T and B cell responses against SARS-CoV-2 are detected in the blood around one week after the onset of COVID-19 symptoms. CD4+ T cells are responsible for prime both CD8+ T cells and B cells and cytokine production to drive immune cell recruitment. Although this pro-inflammatory profile may be an aggravating factor for immunopathogenesis, CD4+ T cells have been hypothesised to control SARS, as depletion of these cells in mice resulted in slower clearance of the virus from the host and severe lung inflammation [16].

According to these pathogenetic observations, HIV-infected individuals might be at an increased risk of SARS-CoV-2 infection or severe disease, especially individuals with comorbidities, lower CD4 cell counts, or unsuppressed HIV RNA viral load [17]. Conversely, although low CD4 counts were not associated with the incidence of COVID-19, immunosuppression did not seem to affect disease severity.

A good clinical outcome in HIV patients could be related to the immunosuppressive status. Romanelli A et al. [18] hypothesised that patients with impaired immune system, as immunosuppression for solid organ transplantation or HIV infection, could be protected against severe clinical manifestations, despite the susceptibility to SARS-CoV-2 infection. Therefore, a lower active immune status might protect the human body from the immune storm following a severe viral attack. It could be possible that the activation of the immune system enhances the injury caused by SARS-CoV-2 infection, with the patient's worst outcome. The activation of the immune system, especially T cells, represents a landmark of the histological picture of lung injury related to COVID-19. Xu et al. [19] investigated the pathological characteristics of SARS-CoV-2 infection by human post-mortem biopsies. They found that histological picture of lung injury related to SARS-CoV-2 infection is similar to Acute Respiratory Distress Syndrome (diffuse alveolar damage, cellular fibromyxoid exudates, desquamation of pneumocytes and hyaline membranes). Besides, they analysed the characteristics of peripheral CD4 and CD8 T cells. They found a hyperactivated status, with an increased concentration of highly pro-inflammatory CCR6+ Th17 in CD4 T cells. The authors concluded that the overactivation of T cells accounts partially for severe immune injury.

Zhu et al. [17] reported the first case report of SARS-CoV-2 infection in a patient with HIV, with a good clinical outcome. Joob et al. (Joob and Wiwanitkit, 2020) noted that the patient did not receive antiviral therapy for HIV infection before. The last aspect is fascinating because it seems that patients never treated for HIV-infection (naïve), despite impairment in lymphocyte count and function, can present a better clinical outcome during SARS-CoV-2 infection. A possible explanation is that in naive HIV infected patients, the uncontrolled viral replication causes lymphopenia and alters the immune system's hyperactive response to SARS-CoV-2 infection. When the antiretroviral treatment started (lopinavir/ritonavir) as management of SARS-CoV-2 infections, it could play a double effect: inhibition of SARS-CoV-2 replication, facilitating the viral clearance; inhibition of HIV replication, that could allow a slight activation of the immune response, just enough to contrast the SARS-CoV-2 infections without the beginning of the hyperinflammatory state [20].

Table 1. The table resumes the available data about HIV patients with SARS-CoV-2 infection.

Autor	No. patients	Age and sex	Comorbidities	Diagnostic test	Previous diagnosis of HIV	Antiretroviral regimen	Treatment
Vizcarra P et al. [9]	51 (35 confirmed; 16 suspected)	Mean age of 53.3, mainly males	63% least one comorbidity	Naso-pharyngeal swab RT-PCR positive	YES	73% tenofovir containing regimen, 22% PI† containing regimen	Different treatments
Gervasoni C et al. [39]	47 (28 proved and 19 suspected)	Mean age of 51±11, mainly males	64% least one comorbidity	28 patients resulted in throat swab RT-PCR positive	YES	80% INI‡-containing regimen, 11% PI containing regimen, 42% tenofovir based regimen	Different treatments
Harter G et al.[40]	33	Mean age of 48 (26-82), mainly males (30/33)	60% (20/33)	29 patients resulted in nasopharyngeal swab RT-PCR positive: 2 bronchoalveolar lavage or sputum	YES	22 tenofovir based regimen; 4 DRV§	ND*
Shalev N et al. [41]	31	Mean age of 60.7, mainly males (24/31)	Different (mainly hypertension, diabetes and obesity)	ND	YES	Different regimen	Different
Childs K et al. [42]	18	Mean age of 52, mainly black males	Obesity in the majority of the population	Naso-pharyngeal swab RT-PCR positive	YES	ND	ND
Guo W et al. [43]	14	Mean age of 56 (31-71), mainly males (13/14)	Five patients: hypertension	ND	YES	ND	ND
Suwanwongse K et al. [44]	9	Mean age of 58 (31-76), mainly males (7/9)	Different (mainly hypertension, diabetes and obesity)	Naso-pharyngeal swab RT-PCR positive	YES	Different regimen	Different treatment
Ridgway JP et al. [45]	8	ND	ND	ND	YES	ND	ND
Guo W et al. [28]	8	Mean age of 57 (47.5-61.5)	ND	ND	YES	2 NRTI¶ + 1 NNRTI**	ND
Blanco JL et al. [7]	5	Mean age of 38 (29-49), 3 male and 2 transgenders	None in three patients, hypothyroidism and asthma in the other two	Naso-pharyngeal swab RT-PCR positive	YES for 4 patients	Different regimen: two patients with Tenofovir/FTC†† and DRVc‡‡; two patients with ABC§§/ 3TC¶¶/DTG***)	Different, with switch ART††† (see review)
Aydin OA et al. [46]	4	Mean age of 37 (34-44), all male	Different in only two cases (first: HBV; second: obesity and diabetes, BPCO, hypertension)	Naso-pharyngeal swab RT-PCR positive	YES	Different (first: none; second: Tenofovir/FTC + DTG; third: Tenofovir/FTC + elvitegravir/ cobicistat; fourth: Tenofovir/ FTC + elvitegravir/cobicistat)	Different (first: Tenofovir/ FTC + LPVr‡‡‡, azithromycin; second: Hydroxychloroquine, azitromycin, oseltamivir; third: Hydroxychloroquine, oseltamivir; fourth: Hydroxychloroquine, azitromycin, oseltamivir)
Riva A. et al [47]	3	Mean age of 60, mainly males	Different in only two cases (hypertension)	Naso-pharyngeal swab RT-PCR positive	YES	Different, all including DRV	Different treatment, with switch ART in two cases
Chen J et al. [25]	1	24, male	ND	Oro-pharyngeal swab RT-PCR positive	YES	3TC, tenofovir, efavirenz	LPVr, interferon inhalation
Coleman H et al. [48]	1	55, male	asthma	Naso-pharyngeal swab RT-PCR positive	YES	Tenofovir/FTC and RAL¶¶¶	ND
Di Giambenedetto S et al. [49]	1	75, male	hypertension	Naso-pharyngeal swab RT-PCR positive	YES	Tenofovir/FTC and RPV§§§	switch ART with Tenofovir/ FTC and DRVc, hydroxychloroquine, sarilumab
Mahmood K et al. [50]	1	54, male	Coronary heart disease, diabetes mellitus	Naso-pharyngeal swab RT-PCR positive	YES	Tenofovir/FTC and DTG	hydroxychloroquine
Nakamoto T et al. [51]	1	28, male	HBV infection	ND	YES	none	hydroxychloroquine
Sun LJ et al. [52]	1	37, male	ND	Naso-pharyngeal swab RT-PCR positive	YES	Tenofovir/FTC and RPV	None, because the illness was mild
Wang M et al. [23]	1	37, male	NO	Antibody positive, RT-PCR negative	NO	NO	Corticosteroids, tocilizumab
Zhao J et al. [24]	1	50, male	ND	Antibody positive, RT-PCR negative	YES	3TC, tenofovir, efavirenz	human immunoglobulin, methylprednisolone, and inhaled interferon alpha-2b
Zhu et al. [17]	1	61, male	diabetes	Naso-pharyngeal swab RT-PCR positive	NO	NO	LPVr, γ-globulin, corticosteroids

Wu Menghua et al [53]	1	49, female	ND	Naso-pharyngeal swab RT-PCR positive	YES	Efavirenz, Zidovudine 3TC	Different: (First: cefuroxime + traditional Chinese medicine second: interferon atomization + ribavirin +abidol + moxifloxacina
Sigel et al [12]	88	25 females, 63 males	Different (mainly hypertension, diabetes and obesity	Naso-pharyngeal swab RT-PCR positive	YES	Different: 78% INI, 17% PI	Different: Hydroxychloroquine Azithromycin Tocilizumab Experimental and expanded- access agents
Hsi-en Ho et al. [13]	93	26 females,67 males	Different (mainly hypertension, diabetes and lung disease, asthma, or COPD	Naso-pharyngeal swab RT-PCR positive	YES	62 of 89 (69.6%) ART regimen that included tenofovir, and 12 of 89 (13.5%) were on a regimen including a PI	Different: azithromycin or hydroxychloroquine steroids
Toombs et al [54]	3	2 male 1 female	Different: (mainly T2DM Hypertension)	Naso-pharyngeal swab RT-PCR positive	YES	RAL+ABC/3TC FTC+TDF+DTG FTC+TNF+NVP****	Different: Antibiotics steroids
Marimuthu et al [55]	6	3 males, 2 females 1 transgender	Hypertension	Naso-pharyngeal swab RT-PCR positive	YES	3TC/NVP/AZT†††† EFV‡‡‡‡/3TC/TDF ATVr§§§§+TDF+3TC	Different:g Paracetamol, vitamin supplements

*not available; †Protease inhibitors; ‡Integrase inhibitor; §Darunavir; ¶ Nucleoside Reverse Trascriptase Inhibitor; ** Non Nucleoside Reverse Trascriptase Inhibitor; †† Emtricitabine; ‡‡ Darunavir/cobicistat; §§ Abacavir; ¶¶ Lamivudine; *** Dolutegravir; ††† Antiretroviral Therapy; ‡‡‡ Lopinavir/ritonavir; §§§ Rilpivirina; ¶¶¶ Raltegravir; **** Nevirapine; †††† Zidovudine; ‡‡‡‡ Efavirenz; §§§§ Atazanavir/ritonavir.

The relationship between HIV-infection naive status, SARS-CoV-2 infection and clinical outcomes is still unclear but particularly interesting. At present, in the literature, do not exist studies that investigated this topic. Further studies should clarify the effect of immunosuppression on the risk of SARS-CoV-2 infection and clinical outcomes.

Peculiar clinical aspects

HIV-infected individuals seemed to be similarly affected by SARS-CoV-2 compared with the general population about clinical presentation. In line with large-scale studies, fever, myalgia, cough, fatigue were typical symptoms of COVID-19. Diarrhoea is an uncommon symptom, reported in 3.8% of patients. Since the beginning, it was observed that low lymphocyte count was common in SARS-CoV-2 infected patients and lymphopenia correlated with disease severity. Lymphocytes in patients with COVID-19 might gradually decrease with the disease progression [21]. Even though HIV infection can cause lymphopenia, in PLHIV and COVID-19, lymphopenia was frequently detected, as in the general population [22].

Comorbidities were risk factors for COVID-19 in the general population, as well as in the HIV-infected population. The mean age of PLHIV with confirmed COVID-19 was slightly lower than the general population, and most cases occurred at age 50-59 years, whereas in the general population, the distribution of COVID-19 was more uniform across age group. Comparing the clinical characteristics, treatment or outcome, there were no significant differences in individuals with CD4 counts less than 200 cells per μL with those with recent CD4 counts of at least 200 cells per μL [9].

Based on these data, PLHIV may not have a significantly higher risk of infection or mortality from SARS-CoV-2.

Peculiar diagnostic aspects

The SARS-CoV-2 virus nucleic acid real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test from the nasopharyngeal swab is the gold-standard for the diagnosis of SARS-CoV-2 infection [23]. The serologic test (antibody IgM and IgG) correlates with the adaptive immune response and can indirectly confirm a previous and/or actual contact with the virus [24].

The use of these diagnostic methods does not differ in the HIV population from the general population, even if in literature, there are described two atypical diagnostic situations of SARS-CoV-2 in patients HIV-infected. Zhao et al. [24] described the case of one patient with a previous travel history in the epicentre of COVID-19, Wuhan, China, and typical clinical presentation of the disease (fever and interstitial pneumonia on computed tomography). The RNA test for SARS-CoV-2 resulted consistently negative on different samples and various occasions, but anti- SARS-CoV-2 antibodies were positive. The authors concluded that the serological test, together with the typical clinical presentation, could confirm the diagnosis of SARS-CoV-2 infection. A potential explanation of this condition is that ART has an anti-SARS-CoV-2 effect. Another hypothesis is that type I interferon (IFN-I) may help suppress SARS-CoV-2 replication. HIV-1 infection can induce higher IFN-I levels, which can help to eliminate SARS-CoV-2, thus leading to persistently undetectable RNA.

Wang et al. [23] described a similar case of SARS-CoV-2 infection in a patient with HIV coinfection not previously diagnosed. The RNA test was negative, but the serologic test confirmed the clinical suspect during the longer clinical course. The presence of two viruses, HIV and SARS-CoV-2, that impaired the immune response could justify the longer course of disease with a persistent presence of specific antibody in the blood.

Regarding the radiologic aspects of COVID-19 pneumonia, computed tomography typical findings are ground-glass opacity, followed by consolidation and interlobular septal thickening. Chen et al. [25] described a case of atypical presentation of COVID-19 pneumonia in a patient HIV positive. They showed patchy shadows in the peripheral lung, involving the interlobar fissure and quick absorption of pulmonary lesions. In this case, the authors supposed that tenofovir, as a component of the antiretroviral regimen, could positively affect the clinical disease's rapid resolution.

Hypothetical therapeutic approach

Knowledge about the efficacy of different antiviral treatments against SARS-CoV-2 is evolving rapidly. Local protocols and guidelines have been periodically updated, even if the therapeutic approach of PLHIV does not differ from the general population until now. There was no evidence that any specific antiretroviral drug-affected COVID-19 severity. Controversies exist regarding the role of some antiretrovirals in preventing or treating SARS-CoV-2 infection. One obvious hypothesis as to this apparent lack of HIV-related risk for the development of severe or critical COVID-19 is ART's protection.

Lopinavir (LPV) is a protease inhibitor (PI) previously authorised to treat HIV infection. LPV was associated with substantial clinical benefit among SARS-CoV infected patients, and it is being studied in MERS-CoV infection [26]. Therefore, during the early outbreak in Wuhan, China, the antiretroviral regimen was used as an off-label treatment for COVID-19. In Thailand, where there is a high prevalence of HIV infection and the use of lopinavir/ritonavir is now common, Joon et al. [27] reported no case of SARS-CoV-2 infection in PLHIV. The authors supposed a protective effect of PI for PLHIV during the pandemic. Also, Guo and colleagues [28] reported that no cases of COVID-19 had occurred among 199 HIV-infected individuals taking ritonavir-boosted lopinavir (LPVr) or integrase inhibitors (INIs). In contrast, eight of 947 individuals taking nucleoside reverse transcriptase inhibitors (NRTI) plus non-nucleoside reverse transcriptase inhibitors (NNRTI) were infected. These observations were not confirmed by a randomised controlled trial, including approximately 200 patients, quickly performed in China, highlighting that the combination of LPVr was not beneficial than the standard of care alone in COVID-19 management [29].

Tenofovir is a nucleotide analogue with activity against DNA and RNA-dependent DNA polymerases preventing the viral replication [30], and its structure and function are remarkably similar to those of Remdesivir. This last drug (also GS-5734) is a monophosphoramidate prodrug of an adenosine analogue with a broad antiviral spectrum. In vitro study suggested that Remdesivir, Tenofovir and other nucleotide analogues were potent drugs with binding-activity on SARS-CoV-2 polymerase [31].

Thus, the PLHIV with COVID-19 pneumonia receiving ART may have moderate symptoms and display faster improvement than the general population and show unconventional radiologic features [25]. Ongoing trials assess the role of tenofovir as a potential strategy for COVID-19 pre-exposure prophylaxis (NCT04334928).

Analysing the clinical published cases of coinfection HIV/SARS-CoV-2, we observed that the authors usually did not switch the previous ART in PLHIV when SARS-CoV-2 was diagnosed. Antiretroviral combinations should not be changed in an attempt to treat SARS-CoV-2 infection because, currently, neither drug combination is considered as a first-line choice for COVID-19 disease in most guidelines for HIV, while changing treatment could lead to increased rates of adverse events. However, in five HIV-positive patients infected by SARS-CoV-2 reported by Blanco et al. [7], four patients resulted in viral suppression with effective ART. Two patients had an antiviral regimen containing PI (darunavir-boosted cobicistat, DRVc) and two an INI based regimen (dolutegravir, DTG). Only one patient was ART naïve. On the day of diagnosis, all patients started anti-SARS-CoV-2 treatment containing boosted-protease inhibitor based on the hypothetical action against coronavirus's protease. In details, three patients received LPVr and two DRVc. Nevertheless, on admission, two patients were on treatment with tenofovir alafenamide fumarate(TAF)/emtricitabine (FTC) as a backbone, and the other two patients with abacavir (ABC)/lamivudine (3TC), following the ART switch for SARS-CoV-2, the patients indicated as "patient 2" and "patient 4", in previous treatment with ABC/3TC, switched to tenofovir disoproxil fumarate (TDF)/FTC. "Patient 3", treated with TAF/FTC, also switched the backbone to TDF/FTC. "Patient 1" confirmed the previous ART (TAF/FTC/DRVc), and the naïve, "patient 5" started the same treatment. Patients on TAF based regimen, on admission, had mild SARS-CoV- 2 infections (upper respiratory infection, no evidence of abnormal findings at chest-X ray, without clinical and laboratoristic alterations) and better clinical outcome. The authors did not clarify the reasons for these choices. One can hypothesise that they could prefer to avoid the combination of ABC with azithromycin and hydroxychloroquine for the higher risk of cardiovascular events derived by drug association [3,32] and that they choose tenofovir disoproxil difumarate (TDF) as the backbone in the antiviral regimen, probably for structural and functional analogies with remdesivir [33-35]. These suggestions are supported by the evidence that HIV specialists prefer to use tenofovir alafenamide fumarate (TAF) for its better safety profile (low risk of renal failure in frail patients) [36] and the major intracellular concentration [37]. In this report, the authors prescribed TDF, possibly for previous better experience combined with LPVr, and better interactions with drugs not mentioned in the article [35].

Nelfinavir, another PI, that in the past was prescribed for the treatment of HIV infection presents *in vitro* direct antiviral activity against SARS-CoV-2. It inhibits the link of SARS-CoV-2 S glycoprotein with endosomal membranes after virion endocytosis, and therefore it blocks the fusion of coronavirus with endosomal cells and the consequent formation of syncytia. At the moment, there are not reported experiences about the use of nelfinavir in clinical practice [38].

Conclusion

Despite the lack of specific studies, PLHIV should not be considered protected from SARS-CoV-2 infection or as having a lower risk of severe disease. Indeed, it is unclear if those with low CD4 cell counts, such as naïve HIV-patients, might have worse outcomes than individuals with restored immunity. Moreover, the clinicians should pay attention to uncommon clinical onset, clinical pictures and diagnosis in this cluster of patients. Globally, because neither drug can be considered a first-line choice in most guidelines for treating SARS-CoV-2 infection, PLHIV should receive the same treatment approach as that applied to the general population. Further well-designed epidemiological and clinical trials are needed to elucidate these aspects.

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Author Contributions

All authors equally contributed to writing the article.

Conflict of interest

The authors declare no conflict of interest.

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