COVID-19 and HIV

COVID-19 Y VIH

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Abstract

Throughout the COVID-19 pandemic, the main risk factors associated with the progression to severe disease or death have been typically advanced age, diabetes mellitus, obesity, high blood pressure, heart disease, and chronic pneumopathy. Because of their immunosuppression status, persons with HIV were also expected to have a higher susceptibility to infection or a poor clinical evolution. So far, this has not been confirmed to happen, giving way to hypotheses about the role of immunosuppression or the use of antiretrovirals, which could explain this paradox. In this article we present the existing data on the epidemiology and characteristics of HIV-COVID-19 co-infection, discuss the available evidence on the possible factors involved in the evolution of individuals affected by both viruses, analyze other determinants that may negatively affect persons with HIV during the pandemic, and present recommendations for the prevention and care of COVID-19 infection in the context of HIV.

Resumen

A través de la pandemia por COVID-19, los factores de riesgo que se han asociado con progresión a enfermedad severa o muerte han sido característicamente la edad avanzada, diabetes mellitus, obesidad, hipertensión arterial, cardiopatía y neumopatía crónica. Por su condición de inmunosupresión, se esperaba que las personas viviendo con VIH (PVV) también presentaran una mayor susceptibilidad a la infección o una pobre evolución clínica. Hasta el momento no se ha confirmado que esto suceda, dando paso a hipótesis sobre el papel de la inmunodepresión o el uso de antirretrovirales, que podrían explicar esta paradoja. En este artículo presentamos la información que existe hasta el momento sobre la epidemiología y características de la coinfección VIH/COVID-19, discutiendo la evidencia disponible sobre los posibles factores implicados en la evolución de los individuos afectados por ambos virus, analizamos otros determinantes que pueden afectar de forma negativa a las PVV durante la pandemia y presentamos recomendaciones para la prevención y el cuidado de la infección por COVID-19 en el contexto de VIH

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Introduction

SARS-CoV-2 infection, the name given to the new coronavirus, and the disease resultant from this virus, coronavirus disease 2019 (COVID-19), has been declared a global health emergency categorized as a pandemic by the World Health Organization (WHO) [1]. Like other coronaviruses, SARS-CoV-2 infects the epithelial cells of the pulmonary alveoli, producing pneumonia, although some reports have described infection in different organs and systems, including gastrointestinal symptoms, especially in children [2]. Although the mortality of the infection is around 5.6% currently [3], the actual burden of the disease is not yet known, and recent reports have estimated that 81% of those infected develop mild symptoms, while 14% have severe symptoms, and 5% become critically ill [4]. As we learn more about the epidemic and infection, we have been able to establish that the most severe cases and mortality are associated with underlying health conditions, the most common being hypertension, diabetes, and cardiovascular disease [5]. Under these circumstances, centers and clinicians around the world have wondered if there is an increased risk of morbidity and complications in immunocompromised patients [6]. Based on the above, we consider the following review to assess current evidence regarding the impact and possible recommendations of care in an immunosuppressed population, such as that of persons with HIV. To develop the review, we relied on a series of clinical questions that allowed us, as of April 6, 2020, to develop a search for scientific literature that would help us answer them. The search was carried out on PubMed and a review of conferences, expert commentary, and recommendations in international scientific societies. Table 1 shows the search equation used in PubMed for answering the revision questions.

In patients with HIV-1 or HIV-2, what has been the epidemiology related to Coronavirus infection?

Little data is found about the impact of coronavirus infections on persons with HIV. A study in a Swiss cohort of HIV-infected patients, in which bronchoalveolar wash samples were tested for respiratory viruses, described coronaviruses and influenza A viruses as the most common [7]. On the other hand, reviews assessing the rate of fatality due to acute respiratory infections among persons with HIV, have reported an increased risk in this group of people compared to those without such comorbidity, although without a difference in the viral etiology of the respiratory infection [8]. Additionally, from the follow-up results of previous epidemics for Acute Severe Respiratory Syndrome (SARS), we know that persons with HIV were not the worst prognosis [9] and that one of the drugs used for their treatment, ritonavir-enhanced lopinavir protease inhibitor (LPV/r) in combination with ribavirin, could help decrease the incidence of failure and death in this scenario [10].

In patients infected with HIV-1 or HIV-2, what has been the epidemiology related to COVID-19 infection?

The pathogenesis of coronaviruses includes the deterioration of the immune response, especially of T lymphocytes, observing a numerical and functional depletion of LTCD4+ and CD8+ T Lymphocytes (LTCD8+), likely to be associated with a negative regulation caused by increased TNF-A, IL-6, and IL-10 [11]. Besides, lymphopenia has been identified as a poor prognosis factor for evolution to Acute Respiratory Failure (IRAG) and death [12]. However, in the description of several series and case reports, HIV has not been identified as common comorbidity in COVID-19 patients, with nonexistent cases of this co-infection in some scenarios [13], or few, including a case report describing a 61-year-old man, residing in Wuhan District, China, with a history of type II diabetes and heavy smoking, who due to

Table 1. Search equations used in PubMed to solve the review questions

Question	Search terms
In patients infected with HIV-1 or HIV-2, what has been the epidemiology related to Coronavirus infection?	((HIV[Title/Abstract] OR HIV-1[Title/Abstract] OR HIV-2[Title/Abstract]) AND (Epidemiology[Title/Abstract] OR Morbidity[Title/Abstract] OR Mortality[Title/Abstract]) AND (Coronavirus[Title/Abstract] OR Middle East Respiratory Syndrome Coronavirus[Title/Abstract] OR (SARS virus[Title/Abstract]))
In patients infected with HIV-1 or HIV-2, what has been the epidemiology related to COVID-19 infection?	((HIV[Title/Abstract] OR HIV-1[Title/Abstract] OR HIV-2[Title/Abstract]) AND (Epidemiology[Title/Abstract] OR Morbidity[Title/Abstract] OR Mortality[Title/Abstract]) AND (COVID-19[Title/Abstract])) HIV AND COVID-19
In patients infected with HIV-1 or HIV-2, what therapeutic options are available for coronavirus co-infections?	((HIV[Title/Abstract] OR HIV-1[Title/Abstract] OR HIV-2[Title/Abstract]) AND (Therapeutics[Title/Abstract] OR Anti-HIV agents[Title/Abstract]) OR (Antiviral agents[Title/Abstract]) AND (Coronavirus[Title/Abstract] OR Middle East Respiratory Syndrome Coronavirus[Title/Abstract] OR SARS virus[Title/Abstract] OR COVID-19[Title/Abstract]))

his respiratory symptoms was diagnosed with COVID-19 and at the same time with HIV infection, and who within treatments received during hospitalization, had LPV/r, recovering satisfactorily from his symptoms [14]. In an attempt to conduct a more systematic search, 1,178 persons with HIV were assessed in Wuhan, of which 12 had suggestive symptoms, and 8 received confirmation of SARS-CoV-2 infection. Of these, 6 had a CD4+ T-cell count (LTCD4+) greater than 350 cel/L and two people had it between 101-350 cel/L; his age was between the ages of 47 and 61; all had HIV-1 RNA <20 copies/ml, and were on treatment based on reverse transcriptase inhibitors nucleotide analog and non-nucleotide analogs; 6 of the patients had mild symptoms, one was classified as with severe symptoms and one patient died [15]. More recently, Blanco *et al.*, reported five HIV cases from 543 consecutive admitted patients with SARS-CoV-2, all of them were male born, 29 to 49 years old, one patient was an advanced late presenter with CD4 13 cel/uL, and four were virologically suppressed at least 7 years on HAART, two with darunavir-boosted cobicistat and two dolutegravir based ART. CD4 cell counts were above 400 cells per uL in all subjects. All patients had COVID-19 clinical pictures resembling the general population, and none of these has died [16].

On the other hand, there has been speculation about possible similarities between HIV-1 and COVID-19 proteins, which after analyzing the suggested sequences shared, were specific to either of the two viruses [17]. In other series, persons with HIV have represented between 0-1.4% [18-21]. These studies draw attention to the apparent lack of association between HIV and an increased risk for progression to IRAG or death, questioning even whether the risk could be even lower than in the general population. In such studies, factors such as low LTCD4+ count, high HIV RNA level, or antiretroviral regimen have not been identified as apparent risk factors.

Among the possible causes that explain these findings, could be differences in receptors through HIV and pathogenic coronaviruses enter the target cell in humans, or, the form of assembly and encapsulation of each virus, since HIV is performed near the cytoplasmic membrane, and in coronavirus, the process is carried out in the endoplasmic reticulum, which may represent that there is no synergistic or cooperative pathogenesis [22].

In persons with HIV-1 or HIV-2, what therapeutic options are available for coronavirus co-infections?

At the time of writing this paper, there are 1,518 clinical studies inscribed clinicaltrials.gov, including most designed to establish the effectiveness of various medicines in the treatment of COVID-19. Strategies based on umifenovir (Arbidol), LPV/r, ribavirin plus interferon-alpha 1b, darunavir/cobicistat, baloxavir marboxil, azvudin, remdesivir, hydroxychloroquine; however, most of these studies are planned to end in one to 11 months, and the results will be only known at the end of this time or through internal analyses [23]. The most promising antiviral is remdesivir, an adenosine nucleotide-like pro-drug with broad-spectrum antiviral action that has been shown in non-human primates that it can prevent viral replication into respiratory tissue and the evolution of clinical symptoms [24], and already has human safety studies [25]. No clinical studies discussing specific therapy of COVID19 or other Coronaviruses in persons with HIV are available; however, the question about the relationship between therapeutic options for COVID-19 treatment and antiretroviral drugs has generated a lot of interest. Patients infected with SARS, who received LPV/r in combination with ribavirin, had lower mortality and severe respiratory distress syndrome, compared to historical controls [26]. In MERS, the combination of Ribavirin and Interferon-b has shown increased in-vitro antiviral activity compared to LPV/r [27]. Based on this, the initial results of a systematic review on this topic have recently been published, in which 22 observational studies and a clinical trial conducted to assess the effectiveness of the use of antiretrovirals in these infections have been published; of the 20 studies that reported outcomes, three did so with SARS, 6 with MERS and 11 with COVID-19, most using LPV/r; however, all studies had limitations in terms of having a small sample size, and having no control group, except in two studies wherein one, the controls were historical [28]. In the only randomized clinical trial conducted with the use of antiretrovirals, 99 patients with severe COVID-19 infection were randomly assigned to receive LPV/r plus the treatment standard for 14 days and 100 patients to receive the standard of treatment, which could include one or more treatments between supplemental oxygen, invasive and noninvasive ventilation, antibiotics, vasopressors, renal replacement therapy, and oxygenation through an extracorporeal membrane. 28-day mortality was numerically lower in the group receiving LPV/r (14/99 compared to 25/100); however, this was not statistically significant. The use of LPV/r was not associated with differences in time to clinical improvement, albeit its use within the first 12 days of symptoms reduced the time to clinical improvement, stay in ICU in 5 days and mortality [29]. The use of other protease inhibitors in combination with ritonavir or cobicistat has been postulated; however, there is no evidence of clinical or in vitro activity against SARS-CoV-2, and some of them may have interactions with drugs used in conditions such as hypertension and diabetes [30]

Role of antiretrovirals in the prophylaxis of COVID-19 infection

One theory to explain the low proportion of HIV/COVID-19 co-infection cases has been the possible protective role of antiretrovirals as prophylactics. So far, there is no clarity whether protease inhibitors can inhibit cysteine 3-protease, similar to chymotrypsin, an enzyme involved in the maturation of SARS [31] Additionally, a large proportion of patients receive antiretroviral therapy (ART) schemes based on Non-Nucleoside Reverse Transcriptase Inhibitors (ITRNn) or integrase inhibitors, which could suggest that there is another cause related to the apparent lower risk of infection and evolution to IRAG. Two studies have assessed a possible protective effect of LPV/r as post-exposure prophylaxis in SARS and MERS infections; however, variations in design and limitations in sample size, as well as lack of information about the intensity of exposure, do not allow conclusions to be drawn as to this effect [28].

Discussion

Based on the previous review, we consider that with the available evidence, it is possible to advance some discussions against the following topics:

Prevention and care of COVID-19 infection in persons with HIV

Prevention

In general, the recommended precautions for reducing exposure to COVID-19 are the same for the entire population, bearing in mind that education should have an emphasis on population groups that have shown greater susceptibility so far. Concerning sexual transmission, as with other coronaviruses, there is no clear evidence today that SARS-CoV-2 is transmitted by this route; however, we consider this to be of little relevance in assessing the risk of a sexual relationship with an infected person, given that current recommendations for COVID-19 prevention are broadly restrictive according to the most important routes of transmission. In China, transmission among household members was the main source of new infections [32], and sex is probably not an additional risk factor. Persons with HIV should continue to be advised for consistent condom use with the same approach they have had for preventing new HIV infections and other sexually transmitted infections (STIs) and exchanging HIV viral populations with different resistance profiles. On the other hand, one concern is that the socio-economic situation, migrant population, and weak health care system in some regions may not make feasible the compliance with prevention measures in the most vulnerable population.

Treatment. Patients diagnosed with COVID-19 who do not require hospitalization should follow the same recommendations for the general population, maintaining antiretroviral therapy, and other prescribed treatments. If the patient requires hospitalization, they should continue their ART unchanged. For critical patients who need enteral feeding, consider liquid presentations of antiretrovirals if available or consult if the antiretroviral in use may be disintegrated for administration, as some cannot be macerated.

Whenever a treatment is formulated for COVID-19, whether approved or under investigation, perform the interaction check on an updated online tool as www.covid19-druginteractions. org. Persons with HIV should not be excluded from clinical studies.

Similarly, in the management of the acute COVID-19 patient with HIV infection, the ART receiving should be evaluated, and the addition of lopinavir/ritonavir to a regimen based on ritonavir or cobicistat-enhanced protease inhibitor should be considered. QT prolongation has been reported with the use of LPV/r, so it should be closely monitored when combined with other medicinal products with a similar effect, such as chloroquine and azithromycin [33].

Challenges facing the fight against HIV in the context of the COVID pandemic 19

The COVID-19 pandemic will not only impact already diagnosed persons with HIV but could have a negative impact on the 90-90-90 UNAIDS strategy, which aims to end the AIDS epidemic. A decrease in the diagnosis of new cases could be expected with the consequent increase in late diagnosis in the medium and long term, taking into account psychosocial risks and interruption of health services, both for control and early diagnosis. It is important to assess the potential risk of decreased availability of HIV RNA as a treatment control test, taking into account increased use of polymerase chain reaction (PCR) equipment for the diagnosis of COVID-19 and the unavailability of alternatives such as performing this test by GeneXpert's technique. In this regard, the high number of people requiring stricter periodic face-to-face control, due to the low proportion of virological control in different countries, as well as the restrictions of health personnel for their mobility, trying to maintain a more

effective social isolation, will require the analysis of new alternatives of care that propose proper follow-up, timely delivery of treatment preventing interruptions therein and reducing the risk of COVID-19 contagion.

Prevention of HIV infection is another point to consider. It requires careful analysis, as the saturation of emergency services can lead to difficulties in accessing the post-exposure prophylaxis (PEP) route in cases of occupational and non-occupational exposure, as well as the slowdown of the pre-exposure prophylaxis (PREP) strategy, which is still in the implementation phase in many countries, especially in Latin America.

Strategies to be adopted to minimize the impact of COVID19 between persons with HIV

Based on the above, we recommend to consider the following strategies, at least while there is more and better quality evidence:

Ensuring patient care

- Each service has a different population and socio-economic reality. The team of professionals should focus efforts on preserving patient communication and results for 90-90-90 strategy compliance within the COVID-19 prevention strategy

- To assess the use of strategies that have been suggested and documented so far in health services based on two elements: the use of information and communication technologies (ITs) and the spacing of In-person consultation, consolidating the implementation of telemedicine and telehealth as crucial elements to allow this strategy.

- Each center should develop a contingency plan to ensure that all patients have access to clinical assessment, preferably non-face-to-face care, through resources such as telemedicine, online portals, virtual or telephone messaging, Apps, and other strategies that can support the patient without increase the risk of exposure to SARS-CoV-2.

- In-person consultation in stable, adherent, and virally suppressed patients should be postponed. Routine laboratories should continue to ensure the timely and uninterrupted supply of their treatments.

- Prioritizing face-to-face care for persons with HIV that by their clinical condition requires urgent attention, or in those where this is considered can have a beneficial effect to avoid complications in the short and medium-term.

- - Health centers that maintain face-to-face service for persons with HIV should develop and implement specific routes and prevention measures to ensure the safety of health personnel and patients.

Avoid complications due to failure in adherence to treatment and other interventions

- Delivery of antiretroviral therapy (ART) for several months can increase adherence to treatment, ensure an uninterrupted supply of ARTs and decongest services in preparation for a possible COVID-19 emergency. Also, it would reduce the possible exposure to SARS-CoV-2 among patients who go to health services and among health professionals in charge of their care. - Adopt the Multi-Month Formula System (MMP) and Multi-Month Dispensing (MMD), ensuring that patients have at least 30-day medication and ideally sufficient for 3 to 6 months. Any type of administrative barriers that hinder the implementation of solutions that prevent interrupted treatment should be avoided. - Regarding clinical care, follow-up and treatment recommendations, there is so far no evidence to support the shift from antiretroviral therapy to persons with HIV based on

alleged beneficial or prophylactic effects of antiretrovirals such as LPV/r; therefore patients that have adequate tolerance, adherence and virological control with their current therapy should continue. - There is no evidence about postponing or suspending recommended vaccination schemes for persons with HIV, on the contrary, updating influenza and pneumococcal vaccines may play a protective function. - Prior to prescribing medications, an online search for potential interactions between basic treatments and potential treatments for COVID should be carried out; there are online websites that dynamically updates the information, such as https://www.covid19-druginteractions.orgof the University of Liverpool. - Related to prophylaxis, WHO suggests the strategy of ensuring TMP/s prophylaxis in all patients who tend to decrease CD4 by about 200 cel/L. - Strategies for the cessation of smoking should be concluded as a risk factor for respiratory disease

Ensuring interdisciplinary management

- Persons with HIV have an increased risk of social isolation, and, in this quarantine period, mental health conditions such as suicidal ideation, substance abuse, and anxiety disorder may be exacerbated. Strengthen psychological counseling for the prevention and management of anxiety related to the current pandemic so that the patient continues adherence to their health care.

- Advice to the patient to develop an action plan in case of presenting symptomatology of any kind should be clear regarding the route to follow. Include civil society and organizations that have experience with persons with HIV in the service of this contingency.

- Persons with HIV may require assistance with food, shelter, transportation, and other types of social support during the health crisis. The professional team must detect these needs and do their best to connect them to available social assistance.

Proactive measures for safety and updating the health team

- Health personnel should keep up to date with the continuous information generated on COVID-19, regarding the recognition of symptoms, immediate reports of epidemiological surveillance and possible interactions between drugs to treat such infection and those used for the treatment of HIV infection and prophylaxis or treatment of opportunistic events.

Conclusions

The rapid and progressive expansion of the COVID-19 pandemic globally takes place amid the still-growing HIV pandemic; however, the effects of the interaction of these two infections are not yet clear from the scarcity of data and reports, without an evident negative impact on the health of persons with HIV. The spread of SARS-CoV-2 has mainly reached Asian and European countries with robust and functional health systems, strong economies, and better control of HIV infection in terms of morbidity and virological suppression. In contrast, the COVID-19 pandemic is expected to cause a great health impact on the African continent, particularly for people with HIV. Africa is currently sheltering 70% of the HIV-infected population worldwide, and the highest number of deaths; however, the reason why this continent has a relatively low number of cases of COVID-19 infection is still elusive [34]. It is equally feasible that, in Colombia and Latin America, with high rates of late presentation of HIV infection, mortality, and continued significant distance from the UNAIDS targets of 90 90 90 [35], persons with HIV in the region are particularly vulnerable to the effects of SARS-CoV-2. For this reason, it is a priority to maintain close monitoring in the care of this population

with information and continuing education strategies, emphasizing optimal adherence to ART and measures to prevention against the contagion by monitoring and supporting the multidisciplinary program with optimized communication technologies, to achieve the objectives of early identification of COVID-19 symptoms, its early diagnosis and treatment and the prevention of critical or fatal outcomes by co-infection with this new coronavirus. It is crucial to expand knowledge of the effects of COVID-19 on HIV infection at the local, regional, and global levels.

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