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Pharmacological considerations for the treatment of COVID-19 in people living with HIV (PLWH)

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ABSTRACT

Introduction: When coronavirus infectious disease-2019 (COVID-19) blew up, ill-fated auguries on the collision between COVID-19 and the human immunodeficiency virus (HIV) epidemics loomed.

Areas covered: Data from observational studies suggest similar incidence attacks of SARS-CoV-2 infection in people living with HIV (PLWH) and HIV-uninfected populations. The mortality rate of COVID-19 is similar in both populations too. The authors discuss the role of combination antiretroviral therapy (cART) in preventing infection or reducing COVID-19 severity. They also discuss the pharmacological interventions for COVID-19 in PLWH.

Expert opinion: Management of COVID-19 in PLWH is no different from the general population. It should be based on careful supportive care, emphasizing lung-protective ventilation, and wise pharmacological interventions. The antiviral drug remdesivir and dexamethasone are the only pharmacological interventions with clinical benefit for COVID-19, whereas anticoagulation may prevent thrombotic complications. The experience with using these drugs in PLWH is limited, which prevents from rendering well-founded conclusions. Until more data on COVID-19 in PLWH become available, the best weapons within our reach are sound supportive care and sensible use of RDV and dexamethasone, bearing in mind the potential for drug–drug interactions of most corticosteroids and antiretroviral drugs.

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1. Introduction

Since first being reported in December 2019 in Wuhan, China, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causing the coronavirus disease of 2019 (COVID-19), has spread around the world, becoming a pandemic, affecting more than 31 million people with almost one million deaths in 9 months [1].

The pathogenesis of COVID-19 has been envisaged as the dynamic interaction between four feedback loops, including the viral loop, the hyperinflammatory loop, the non-canonical renin-angiotensin system (RAS) axis loop, and the hypercoagulation loop [2]. Therefore, comprehensive COVID-19 management may need pharmacological measures addressed to counteract these disturbances.

The clinical stages of SARS-CoV-2 infection range from absent or minimal symptoms to severe respiratory failure with multiple organ failure [3]. About 80% of the people have SARS-CoV-2 infection asymptomatic, or with mild to moderate illness (mild symptoms up to mild pneumonia), 15% have severe symptoms (dyspnea, hypoxia, or >50% lung involvement), and 5% have a critical illness with respiratory failure, shock, or multiorgan system dysfunction [4].

The most common symptoms are fever, shortness of breath, cough, fatigue/malaise, headache, and confusion [5]. Among patients with severe disease, the median time to acute

respiratory distress syndrome (ARDS) from the illness onset ranged from 8 to 15 days [5]. Eleven percent of patients need intensive care unit (ICU) admission, usually because of ARDS (18.4%), with a mortality rate of 4.3% [6]. Mortality is higher in ICU patients [4] and those requiring mechanical ventilation (MV) [7]. Increased biomarker and proinflammatory cytokines, as high-sensitivity cardiac troponin I, D-dimer, serum ferritin, interleukin (IL)-6, IL-8 and tumor necrosis factor (TNF)- α , are associated with worse outcomes [5,8–10]. Severe cases have lower lymphocyte, monocyte, eosinophil, and basophil counts, higher leukocyte count and neutrophil-lymphocyte ratio (NLR), and lower levels of both helper T (Th) cells and suppressor T cells [11].

Staged therapeutic management has been proposed early during the pandemic according to the different clinical phases of COVID-19 [3]. In the initial (mild) stage, in addition to symptomatic relief, early treatment with antiviral agents could play a role in reducing the duration of symptoms, minimize contagiousness, and prevent progression to severity. In the second stage (moderate), when inflammation in the lung and hypoxemia is present, corticosteroids may be useful. Finally, in the third and most severe stage of the illness, the use of immunomodulatory agents, such as corticosteroids, cytokine inhibitors, and intravenous immune globulin, has been proposed to reduce systemic inflammation before

Article highlights

- Incidence of SARS-CoV-2 infection and mortality from COVID-19 are similar to those of the HIV-uninfected population
- Combination antiretroviral therapy (cART) does not prevent SARS-CoV-2 infection neither decreases COVID-19 severity
- Careful supportive care and the wise use of remdesivir, dexamethasone, and anticoagulation therapy are the mainstays of COVID-19 management
- There is limited experience with the use of these drugs in PLWH with COVID-19
- A careful acquaintance of the potential interaction between corticosteroids and antiretroviral drugs

multiorgan dysfunction develops [3]. More recently, World Health Organization (WHO) guidelines recommend corticosteroids for the treatment of patients with severe and critical COVID-19 [12].

Current evidence indicates that the risk of severe illness and worse outcomes increases with age, male gender, and comorbidities, such as hypertension, diabetes, cardiovascular disease, chronic lung disease, chronic kidney disease, cancer, and obesity [4,5,8,13–17]. The role of immunosuppression, caused by solid organ transplantation, cancer, immunodeficiency, or medication-induced, is controversial. There is evidence that patients with solid organ cancer and transplantation have more severe disease [17,18]. But generally speaking, there are few immunosuppressed patients with COVID-19, and they present a favorable outcome compared to other comorbidities [19]. A possible explanation for the hypothetical protective role of a weaker immune response is that an exuberant cytokine release is essential in inducing immune-mediated damage.

2. COVID-19 in PLWH

The experience from previous coronaviruses outbreaks like severe acute respiratory syndrome (SARS) and the Middle East respiratory

syndrome (MERS) coronaviruses on the susceptibility and severity disease in PLWH is scarce [20]. People living with HIV (PLWH) could potentially be at increased risk of developing severe COVID-19 disease for various reasons. First, immunosuppression or not receiving combination antiretroviral treatment (cART) and complications from added opportunistic infections could play a negative role. HIV infection remained a significant risk for infectious respiratory diseases (both opportunistic infections and non-acquired immunodeficiency syndrome (AIDS) infections) after the introduction of highly active ART (HAART) [21]. Some of these infections may be even more severe in PLWH [22] and their management remains a large component of HIV healthcare [23]. Persistent risk of respiratory infections in PLWH may be in part due to incomplete penetrance or ART coverage [24]. Even on cART, many PLWH have incomplete immune reconstitution and persistent immune activation [25], which would support a theoretical risk of worse COVID-19 outcomes. HIV infection is also an independent risk factor for other noninfectious pulmonary complications, including chronic obstructive pulmonary disease (COPD), diffusing capacity impairment, asthma, and pulmonary hypertension [24]. Both infectious and noninfectious respiratory diseases were associated with an increased risk of mortality [21,24]. Moreover, PLWH are aging [26], have a higher prevalence of comorbidities [27], and other risk factors for respiratory infections, such as smoking [28], all known conditions associated with increased COVID-19 severity.

Since the beginning of the COVID-19 epidemic, case reports, case series, and cohorts of PLWH with COVID-19 have been published worldwide [29–45]. A systematic review summarized the evidence on the earliest PLWH with COVID-19 [46] to provide updated information and advice to healthcare professionals about emerging patterns. The results of extensive population studies comparing COVID-19 outcomes in patients with and without HIV infection have recently been presented [47–49].

2.1. Prevalence, risk factors, and disease severity

The prevalence of SARS-CoV-2 infection in PLWH ranges from 0.3% to 0.8% [31,34,36,50] and is similar to that in the general population [31,34], or even lower when including suspected

Table 1. Drug interactions between antiretroviral treatment and proposed treatments for COVID-19.

	DTG	BIC	RAL	EVG/c	DOR	RPV	EFV	ETR	ATV/r o c	DRV/r o c	LPV/r	FTC	3TC	ABC	TDF	TAF	MVC
Tocilizumab																	
Sarilumab																	
Siltuximab																	
Ruxolitinib																	
Baricitinib																	
Anakinra																	
Bevacizumab																	
Infliximab																	
Adalimumab																	
Interferon beta-1a																	
Interferon alpha-2b																	
Dexamethasone																	
Methylprednisolone																	
Chloroquine																	
Hydroxychloroquine																	
Azithromycin																	
Remdesivir																	

DTG: dolutegravir. BIC: bictegravir. RAL: raltegravir. EVG/c: elvitegravir/cobicistat. DOR: doravirine. RPV: rilpivirine. EFV: efavirenz. ETR: etravirine. ATV/r o c: atazanavir/ritonavir o cobicistat. DRV/r o c: darunavir/ritonavir o cobicistat. LPV/r: lopinavir/ritonavir. FTC: emtricitabine. 3TC: lamivudine. ABC: abacavir. TDF: tenofovir disoproxil. TAF: tenofovir alafenamida. MVC: maraviroc.

Do not coadminister

Potential interaction

Not interaction expected

cases [33]. Among patients who required hospital admission, prevalence ranges from 0.8% to 2% [16,32,41,42,50], which does not suggest increased hospitalization rates among PLWH [41]. As in uninfected people [4,5,7,13–16], PLWH have higher morbidity and mortality among male patients, and mortality increases with multimorbidity [46]. The risk for SARS-CoV-2 infection and hospitalization is greatest in men older than 70 years [34]. Duration of HIV infection [33], CD4 nadir [33] and recent CD4 count [33,40,42], CD4/CD8 ratio [33] and HIV viral load on or prior to admission [42] are unrelated to COVID-19 severity. The mild CD4 percentage decrease observed in hospitalized PLWH is not associated with worse COVID-19 outcomes [42]. A population-based study in South Africa found a two-fold increased risk of COVID-19 death in hospitalized PLWH with CD4 < 200 cells at diagnosis or admission, while the previous immuno-virological status did not influence mortality [49]. Comorbidities, such as organ transplant, diabetes, and obesity, carried a poor prognosis in some studies [42,47], while not in others [33].

High C reactive protein (CRP) [42,47], procalcitonin [42], IL6 [42], white blood cell (WBC) counts [47] are signals of dismal prognosis. Lower lymphocyte counts and higher lactate dehydrogenase concentrations are markers of severe COVID-19 in PLWH [33]. Distinct therapies resulted in no difference in COVID-19-associated mortality [42].

2.2. Demographics and clinical characteristics

Most PLWH with COVID-19 were males; their mean age was 53 years [46], which is nearly ten years lower than that observed in uninfected patients [7,16]. In a large population-based study, the age difference between the two populations was even greater [47]. Some authors found that PLWH were more likely to be of black ethnicity [47,48] and from socially deprived areas [48]. Comorbidity has been reported in nearly two-thirds of PLWH with COVID-19 [46], a higher proportion than in the general population [5,7,13]. The most common clinical symptoms of COVID-19 in PLWH were fever (74%) and cough (58.3%) [46], as in uninfected patients [6,7,13]. PLWH were more likely to present with systemic symptoms and signs and have a longer duration of symptoms [47]. The severity of the COVID-19 disease was mild in most cases (66.5%) [46], with no significant difference in supplemental oxygen requirement by HIV status [40,42,47].

2.3. Viro-immunological features, biomarkers and imaging

Most PLWH with COVID-19 were cART-treated with suppressed HIV viral load and relatively preserved immunity [46]. Since patients with low CD4 counts are often underrepresented, it could be that uncontrolled HIV infection and poor CD4 + T-cell function may limit SARS-CoV-2-related immune dysregulation and cytokine release. The absence of T-cell activation has been hypothesized to mitigate the severe immunopathological phenomena in COVID-19 [51]. There was CD4 decline (median: 4%, IQR 0%–9%) [42], consistent with lymphopenia, during COVID-19 [11]. Ferritin [42], total white blood cell [42,47] and platelet counts [47], and CRP were higher whereas absolute lymphocyte count [40,47] was lower in PLWH than in uninfected

people. Chest imaging abnormalities were more frequent in PLWH than in uninfected patients [40].

2.4. Outcome

Hospitalization, ICU admission, and case-fatality rates in PLWH with COVID-19 are 64.7%, 16.8%, and 14.3%, respectively [46]. However, there are confounding factors such as older age and a higher prevalence of comorbidities. Furthermore, there might also be higher hospitalization rates among PLWH due to safety reasons. Most studies have included only symptomatic patients, thus overestimating morbidity and mortality. Matched cohorts found no significant differences in adverse outcomes in PLWH for hospitalized COVID-19 patients compared to uninfected patients [40,42].

A larger prospective cohort in Spain found greater age- and sex-standardized mortality from COVID-19 in PLWH (3.7 per 10,000) than in the general population (2.1 per 10,000) [34]. Recently, three population studies from the UK and South Africa concluded that living with HIV raises the risk of dying from COVID-19 (from 1.63 to 2.3-fold increased risk), after adjusting for age and other factors [47–49]. This increased mortality risk was similar in PLWH irrespective of viremia and CD4 count, although there was little representation of virologically uncontrolled and immunosuppressed patients [49].

3. The potential role of antiretroviral therapy (cART) in preventing COVID-19

Regarding the possible beneficial role of antiretroviral use in preventing COVID-19, the observational design and lack of appropriate control of many studies do not permit us to reach reliable conclusions [46]. Larger cohorts and population-based studies in PLWH have demonstrated some evidence of a potential effect of nucleoside reverse transcriptase inhibitors (NRTI) against SARS-CoV-2 infection, finding no benefit of other antiretroviral drugs. A Spanish observational study found lower risk for COVID-19 diagnosis and hospitalization in PLWH receiving tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)-based cART versus those receiving other regimens [34]. Moreover, none of the TDF/FTC recipients died or was admitted to the ICU. In a recently published further analysis, the authors suggest that the association observed is not explained by confounding due to unmeasured clinical characteristics [52].

Other studies found an adjusted association between NRTI use [42], and specifically TDF-based cART [40], with lower COVID-19-related mortality in PLWH. However, the analysis was not subject to correction for multiple statistical tests and could have been confounded by other factors. Results of a retrospective observational study in Lyon evaluating the attack rate of COVID-19 infection in PLWH on cART, including TDF or TAF/FTC-based cART, are still unsettled [53].

No difference has been found in PLWH COVID-19 incidence concerning the other components of cART. Small case-series in PLWH with COVID-19 showed that non-nucleoside reverse transcriptase inhibitors (NNRTI) [31] and darunavir (DRV)-based regimens [35] did not prevent SARS-CoV-2 infection or protect against worsening respiratory function. Other studies

also found no association between previous NNRTI-, protease inhibitor (PI)- or integrase strand transfer inhibitor (INSTI)-based regimens and COVID-19 diagnosis [33], severity [33] or mortality [42,49]. An observational study is assessing the possible impact of ritonavir-boosted lopinavir (LPV/r)-based cART on the attack rate of SARS-CoV-2 infection in PLWH [53].

Until robust evidence from randomized clinical trials (RCTs) becomes available, switching PLWH from their usual cART is not currently recommended. Besides, there is no evidence to support HIV-uninfected people taking antiretroviral drugs to prevent SARS-CoV-2 infection, except in the context of pre-exposure prophylaxis to prevent HIV acquisition or an RCT [54].

4. Pharmacological management of COVID-19

Potential therapies for COVID-19 can be classified into at least four categories depending on the target addressed. The direct-active antivirals target coronavirus components and block its replication. Other drugs may interfere with host factors crucially required for viral infection and replication. Adjunctive therapy modulates the exacerbated host immune response, thereby reducing inflammation and limiting immune-mediated damage. Some drugs exert more than one mode of action [55]. Additional interventions with clinical benefit are those directed to avoid the excess thrombotic risk associated with COVID-19.

4.1. Antiviral agents

The SARS-CoV-2 lifecycle steps provide potential therapeutic targets, including viral entry, RNA synthesis, replication, and assembly process pathways [55–58].

4.1.1. Antiretroviral drugs

Several antiretroviral drugs used for the treatment of HIV infection have been considered for use in the treatment of COVID-19, LPV/r being the most frequently studied. LPV/r is active against HIV and SARS and MERS coronaviruses [59]. LPV/r also has *in vitro* antiviral activity against SARS-CoV-2 [60]. However, the concentration of LPV/r required to inhibit SARS-CoV-2 is 4000- to 8000-fold higher than that required to inhibit HIV [61], which may carry unbearable toxicity. Early in the COVID-19 pandemic, some national guidelines suggested treatment with LPV/r.

Two RCTs on the efficacy of LPV/r in COVID-19 hospitalized patients have been published to date. They found no clinical benefit of LPV/r therapy over symptomatic or supportive care [62,63]. Data from a retrospective analysis of hospitalized COVID-19 patients suggested that early administration (≤ 10 days from disease onset) of LPV/r was associated with a shorter duration of virus shedding [64]. Accordingly, the RECOVERY and the WHO-sponsored SOLIDARITY trials discontinued LPV/r arms in late June and early July 2020, respectively [65,66].

Given the structural similarity with LPV, DRV, boosted with ritonavir or cobicistat, was suggested as a candidate drug for the treatment of SARS-CoV-2 infection. However, DRV has no *in vitro* antiviral activity against SARS-CoV-2 at clinically relevant concentrations [67]. Moreover, DRV (alone or combined

with interferon-alpha 2b) showed no evidence of benefit in terms of SARS-CoV-2 clearance rate or clinical improvement in patients with mild COVID-19 [68]. Notwithstanding that, ongoing trials investigate DRV as a therapeutic option for COVID-19, one of them comparing DRV vs. LPV/r [69]. Currently, the lack of *in vitro* and *in vivo* efficacy does not support DRV use in COVID-19 treatment.

Data regarding tenofovir use against SARS CoV-2 are conflicting. A molecular docking study indicated that tenofovir tightly binds to SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), suggesting that it may inhibit this enzyme [70]. A recent *in vitro* study found that both the active triphosphate form of tenofovir (TDF, tenofovir alafenamide (TAF)), and FTC act as terminators of the RdRp-catalyzed reaction and inhibit this enzyme [71]. Moreover, treatment with TDF plus FTC showed a reduction in severity scores, duration of clinical symptoms, and nasal SARS-CoV-2 titers in infected ferrets [72]. On the contrary, other studies have failed to demonstrate any tenofovir or FTC *in vitro* activity against SARS-CoV-2 [60,73]. Tenofovir has immunomodulatory effects, including reducing inflammatory cytokines IL-8, IL-10, and monocyte chemoattractant protein 1 (MCP-1), but also in IL-12. As IL-10 inhibits and IL-12 regulates the inflammatory and immune responses to viral infections, these results suggest a potential beneficial effect of tenofovir in COVID-19 [74]. There are currently three RCTs investigating FTC plus TDF [75,76] or TAF [77] as prophylaxis for COVID-19 in healthcare workers, one still recruiting [75]. Moreover, as TDF, TAF and FTC (with suggested molecular basis to prevent SARS-CoV-2 infection [70,71,74]) are components of the two approved medications for use as HIV pre-exposure prophylaxis (PrEP), their effect on the risk of COVID-19 is being evaluated in PrEP users [53]. Recently, an observational descriptive study conducted in Madrid found that users of PrEP presented a higher seroprevalence to SARS-CoV-2 than the control group, with no statistically significant differences in relation to COVID-19 clinical manifestations [78].

C–C chemokine receptor type 5 (CCR5) receptor antagonist maraviroc (MVC) has been suggested as a potential drug candidate for COVID-19. MVC binds to the substrate-binding pocket of SARS-CoV-2 main protease and forms a significant number of non-covalent interactions, resulting in potent inhibition and infection prevention [79]. Besides, by inhibiting CCR5, a receptor for molecules that mediate inflammation, MVC could play a beneficial role in treating the inflammatory phase of the COVID-19. A clinical trial evaluating the efficacy and safety of MVC in SARS-CoV-2 infection is currently recruiting patients in Spain [80].

4.1.2. Type I and III interferons

Type I Interferon (IFN) α/β are broad-spectrum antivirals, exhibiting direct inhibitory effects on viral replication and inducing an immune response against viruses [81]. During the 2003 SARS-CoV-1 outbreak in Toronto, Canada, treatment of hospitalized SARS patients with IFN- α , resulted in accelerated resolution of lung abnormalities [82]. IFN- β 1a inhibits replication of SARS-CoV-2 *in vitro* [83]. IFN- β 1a has been used in the treatment of COVID-19, in conjunction with other treatment

regimens, with decreased virologic clearance [84]. The first clinical trial conducted with IFN- β -1a in severe COVID-19 did not find statistically significant differences between the two groups in time to clinical response. The discharge rate increased significantly on day 14 and 28-day mortality decreased, especially when patients received IFN- β -1a early in the disease [85]. Regarding IFN- α -2b, a retrospective study showed significantly reduced detectable virus shedding from the upper respiratory tract [86]. Currently, there is a study with rintatolimod and IFN- α -2b for the treatment of mild or moderate COVID-19 infection in cancer patients [87].

Type III interferon (IFN- λ) also acts as an antiviral, but produces a local response because it is expressed in epithelial cells and a subset of immune cells, including neutrophils [88]. This minimizes systemic inflammation contrary to IFN type I and causes less adverse effects [89]. Currently, there are five ongoing clinical trials with IFN- λ for the treatment or prevention of COVID-19 [87].

There are no known interactions between IFN – 1a and IFN – 2b and cART components. Although co-administration with TDF or TAF has not been studied, a pharmacokinetic interaction is unlikely to occur. It should be noted that liver decompensation has occurred in HIV/HCV co-infected cirrhotic patients receiving NRTI, interferon, and ribavirin. Therefore, these patients need close monitoring [90].

4.1.3. Remdesivir

Remdesivir (RDV) is an intravenous nucleotide prodrug of an adenosine analog. RDV binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. It has a potent *in vitro* antiviral activity against a diverse panel of RNA viruses such as Ebola, Marburg, MERS-CoV, SARS-CoV, respiratory syncytial virus, Nipah virus (NiV), and Hendra virus [91]. It has demonstrated *in vitro* activity against SARS-CoV-2 [92]. In a rhesus macaque model of SARS-CoV-2 infection, RDV treatment was initiated soon after inoculation, and RDV-treated animals had lower lung virus levels and less lung damage than controls [93]. RDV improves pulmonary function, reduces lung viral load, and severe lung pathology in mice [94].

RDV has been studied in several RCTs. In June 2020, the EMA's human medicines committee (CHMP) recommended granting conditional marketing authorization for the treatment of COVID-19 in adults and adolescents older than 12 years with pneumonia who require supplemental oxygen, but who do not require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation [95,96]. The dossier's assessment was mainly based on data from NIAID-ACTT-11, a multinational, randomized, placebo-controlled trial sponsored by the US National Institute of Allergy and Infectious Diseases, plus supporting data from other studies.

NIAID-ACTT-1 evaluated the effectiveness of a planned 10-day course of RDV in over 1000 hospitalized patients with COVID-19 compared with placebo. The primary measure of effectiveness was patients' time to recovery, defined as no longer being hospitalized and/or requiring home oxygen or being hospitalized but not requiring supplemental oxygen

and no longer requiring ongoing medical care. Overall, the study showed that patients treated with RDV recovered after 11 days, compared with 15 days for placebo-treated patients. This effect was not observed in patients with mild to moderate disease. For patients with severe disease, approximately 90% of the study population, time to recovery was 12 and 18 days in the RDV and placebo group, respectively. However, no difference was seen in time to recovery in patients on mechanical ventilation or extracorporeal membrane oxygenation. In a post-hoc death analysis at day 14, there was no evidence that RDV impacted the mortality rate in this subgroup (HR 1.06; 95% CI, 0.59–1.92). Recent data report that the estimates of mortality by day 29 were 11.4% in the RDV group and 15.2% in the placebo group (hazard ratio, 0.73; 95% CI, 0.52 to 1.03) [96–98].

Gilead presented new findings in July on a comparative analysis of Phase 3 SIMPLE-Severe trial and a real-world retrospective cohort of patients with severe COVID-19. In this analysis, RDV was associated with an improvement in clinical recovery and a 62% reduction in mortality risk compared with standard of care [99]. However, the results of SOLIDARITY study, a mortality trial recommended by WHO expert groups in hospitalized COVID-19 of four re-purposed antiviral drugs (RDV, hydroxychloroquine, LPV/r, and IFN- β -1a) showed that no study drug reduced mortality, overall or in any subgroup, or reduced initiation of ventilation or hospitalization duration [100]. Specifically, this preprint included a meta-analysis of mortality of four trials that have compared RDV with control: the Solidarity trial (604 deaths in 5451 randomly assigned patients), the ACTT-1 (136 deaths in 1062 patients; mortality was a secondary outcome), and two smaller trials [101,102] (41 deaths). Summation of these trials showed a rate ratio for death (RDV vs. control) of 0.91 (95% CI, 0.79 to 1.05) [100]. Due to the results from these trials, the WHO guidelines on drugs for COVID-19 suggest against administering remdesivir in addition to usual care for the treatment of patients hospitalized with COVID-19 regardless of disease severity (weak or conditional recommendation) [103].

Treatment starts with a 200-mg infusion on the first day, followed by one 100-mg infusion a day for at least 4 days, and no more than 9 days. A multinational, open-label trial of hospitalized patients with severe COVID-19 showed that RDV treatment for 5 or 10 days had similar clinical benefits [96,97,104]. RDV is a safe drug but can cause gastrointestinal symptoms, elevated transaminase levels, and increased prothrombin time. RDV is not recommended in patients with eGFR < 30 ml/min [105,106]. RDV has no relevant pharmacokinetic interactions with almost any medication [90,106,107]. However, the use of RDV with strong CYP3A4 inducers (e.g. rifampicin) is not recommended since it may modestly reduce RDV levels. Other drugs used for COVID-19 such as chloroquine or hydroxychloroquine may decrease the antiviral activity of RDV, and co-administration is not recommended [108].

Experience with RDV in PLWH is limited and comes from PLWH included in RCT or expanded access programs. The reports range from a single patient to four receiving, moreover, other expanded access drugs such as sarilumab and anakinra [33,41,42]. Co-administration with antiretrovirals has not been studied, but RDV is a substrate of CYP2C8, CYP2D6,

CYP3A4, OATP1B1, and P-gp. Therefore, based on metabolism, clearance, and toxicity profiles, a clinically significant interaction is unlikely [90,107].

4.1.4. Mixed action mechanism drugs (chloroquine, hydroxychloroquine, and azithromycin)

Chloroquine and hydroxychloroquine (HCQ) are antimalarial drugs. HCQ is also used to treat autoimmune diseases. Both increase the endosomal pH, inhibiting the fusion of SARS-CoV-2 with the host cell membranes and also have immunomodulatory effects. Due to these effects, it has been hypothesized that they may be useful in the treatment of COVID-19 [92,109]. Azithromycin (AZR) is a macrolide antibiotic that, *in vitro*, might decrease viral load and might exert immunomodulatory effects [110,111]. An *in vitro* study showed synergistic activity of the combination of HCQ and AZR against SARS-CoV-2 [112], and a small non-randomized, open-label trial from France reported decreased viral load when AZR was added to HCQ in patients with non-severe COVID-19 [113]. Nevertheless, these drugs might increase the risk of ventricular arrhythmias or cardiac arrest due to corrected QT (QTc) interval prolongation, especially when co-administered with other drugs that prolong the QTc interval [114,115].

Most preclinical drug efficacy studies to help guide decisions for COVID-19 treatment have shown the lack of antiviral activity of HCQ in animal models (macaque, hamster) [116–118] and in human cell lines [119].

The safety and efficacy of chloroquine and HCQ with or without AZR were evaluated in RCTs [120–124] and observational studies [125,126]. These studies showed no evidence of benefit and risk of QTc lengthening. Therefore, these drugs are not recommended for the treatment of COVID-19, outside of RCT [107,127]. However, a multi-center retrospective observational study conducted in Michigan reported a survival benefit among hospitalized patients who received either HCQ alone or HCQ + AZR [128]. A higher percentage of patients in the HCQ arms also received corticosteroids compared with the control arm (77.1% vs. 36.5%), and thus, the imbalance in corticosteroid use confounded the results in this study. As well, some authors suggest that anti-inflammatory action of HCQ should not be discarded due to the results observed in some observational studies with early HCQ treatment and low doses that shows lower risk of admission in intensive care unit [129,130] and lower mortality rate in patients exposed to HCQ therapy compared to no or other treatment [129,131–133].

There are no data from RCT on chloroquine, and HCQ + AZR, in treating COVID-19 in PLWH. The scarce data come from case series in which most PLWH received HCQ + AZR. In these retrospective studies, between 17% and 77% of PLWH received HCQ whereas between 15% and 75% were treated with AZR [33,36,41,42]. There were no differences in COVID-19-associated mortality in patients treated with HCQ, AZR, and other expanded access agents [42].

Co-administration of these drugs with cART components has not been studied but based on drug metabolism and clearance, a clinically significant interaction is unlikely. Chloroquine and HCQ undergo metabolism by CYPs 2C8, 3A4, and 2D6, and are eliminated unchanged via the kidney

(50%). No effect on chloroquine or HCQ levels by antiretrovirals is expected. Bictegravir levels may increase due to P-glycoprotein inhibition by chloroquine or HCQ, but this is unlikely to be clinically significant as clinical data have shown a good safety profile up to a 2.4-fold increase in bictegravir area under the curve. Concentrations of tenofovir may also increase, and the recommended dose of 10 mg TAF with P-gp inhibitors is not possible with Biktarvy, which is only available as a fixed-dose combination containing 25 mg of TAF. Thankfully, TAF has an excellent clinical safety profile. No effect on FTC is expected [90,107]. Some PI could potentially increase chloroquine and AZR exposure. There is no dosage adjustment recommended for chloroquine, but toxicity monitoring is advisable. Rilpivirine may lengthen QTc, and when co-administered with these drugs, ECG monitoring is suggested [90,107].

4.2. Immunomodulatory agents

In patients infected with SARS-CoV-2, there is an increase in pro-inflammatory cytokines (IL-6, IL-1, IFN- γ , TNF- α), probably because of activated T-helper-1 cell response [134] and macrophages [135,136]. There is evidence that some COVID-19 patients respond to infection with an exacerbated cytokine release, similar to that seen in bacterial septic processes, which has been associated with the severity of the disease [137]. However, cytokines that suppress inflammation (IL-4 and IL-10) have also been observed by increased T-helper-2 secretion [5]. Some scores have been evaluated that relate levels of cytokines with severity and outcome of SARS-CoV-2 infection, especially IL-6 and IL-10 [10,138]. Therefore, immunomodulatory agents have been proposed as a treatment for COVID-19-associated ARDS.

4.2.1. Interleukin-6 inhibitors

IL-6, a pleiotropic cytokine released by T-cells, endothelial cells, fibroblasts, macrophages, and monocytes during acute and chronic inflammatory disease, regulates the immune system [139,140]. High levels of IL-6 correlated with prognosis of COVID-19, providing the rationale for targeting IL-6 pathway with monoclonal antibodies [141]. Currently, there are 3 monoclonal antibodies capable of inhibiting IL-6 signaling: tocilizumab, sarilumab, and siltuximab [142–144]. Tocilizumab was the first IL-6 inhibitor used in the treatment of COVID-19 in critically ill patients, resulting in decreased oxygen need and decreased pulmonary opacities in lung CT scan [141]. Multiple observational studies have been published describing clinical and laboratory outcomes in COVID-19 patients treated with tocilizumab [145–147]. One of the largest observational studies published to date shows that tocilizumab is associated with a lower risk of death or ICU need in patients with high levels of CRP (>150 mg/L) [148].

There are several ongoing RCTs with tocilizumab, sarilumab, and siltuximab, alone or in combination. Three RCTs about tocilizumab use in COVID-19 have been published recently [149–151]. CORIMUNO-TOCI-1 [149] is a RCT in patients with COVID-19 and pneumonia requiring oxygen support but not admitted to the intensive care unit in France. This

study, with 130 patients, concluded that tocilizumab did not reach the primary outcome, reduce WHO-CPS scores lower than 5 at day 4. But might have reduced the risk of noninvasive ventilation, mechanical ventilation, or death by day 14. Although no difference on day 28 mortality was found. Other RCT was carried out in Italy [150], with 126 patients hospitalized with COVID-19 pneumonia and PaO₂/FIO₂ ratio between 200 and 300 mm Hg. Twenty-eight percent of patients in the tocilizumab arm showed clinical worsening vs 27% in standard of care group. The trial was prematurely interrupted after an interim analysis for futility. The third [151] is a double-blind, placebo-controlled trial involving patients with confirmed severe acute respiratory syndrome SARS-CoV-2 infection. Primary outcome was not achieved with 243 patients. The hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% confidence interval, 0.38 to 1.81; P = 0.64). Therefore, tocilizumab was not effective for preventing intubation or death.

A clinical trial with sarilumab showed that there were no differences in general clinical improvement and mortality compared to standard treatment [152]. In its preliminary analysis, a study with siltuximab, SISCO (siltuximab in severe COVID-19), has reported that it reduces the need for ventilation [153]. There is scarce experience on the use of tocilizumab in PLWH, only 8 patients reported to date [33,36,41].

Tocilizumab, sarilumab, and siltuximab may decrease serum concentrations of CYP3A4 substrates such as atazanavir, DRV, ritonavir, cobicistat, elvitegravir, rilpivirine, efavirenz, etravirine, doravirine, and MVC [154]. In 12 rheumatoid arthritis (RA) patients receiving a single dose of simvastatin (CYP3A4 substrate), the AUC of simvastatin and its -hydroxy metabolite were reduced by 57% and 39%, respectively, 1 week following tocilizumab compared to simvastatin without tocilizumab. Five weeks after tocilizumab infusion, reduced systemic exposure was still evident [155]. Therefore, it is recommended to monitor the effects of antiretroviral drugs if patients receive concomitant treatment with tocilizumab. Regarding sarilumab, the technical data sheet recommends caution when combining sarilumab and CYP3A4 substrates with narrow therapeutic indexes where a decrease in exposure and effectiveness is undesirable [143]. With siltuximab treatment, the decrease in levels of CYP3A4 substrates should be monitored. Once siltuximab is discontinued, the rise in CYP3A4 substrates should also be monitored because restoring CYP3A4 activity may increase the metabolism of CYP3A4 substrates. This effect may persist several weeks after discontinuation due to siltuximab long half-life [156].

4.2.2. JAK inhibitors

Janus kinase (JAK) mediates the release of proinflammatory cytokines leading to increased inflammatory processes [157]. The mechanism of JAK inhibitors, sunitinib, erlotinib, ruxolitinib, fedratinib, and baricitinib, is inhibition of cytokine signaling, thereby downregulating the immune response. The doses of sunitinib and erlotinib needed to inhibit AP2-associated kinase 1 and cyclin G-associated kinase are significantly higher than those used for anticancer treatment, which may result in unbearable adverse effects [157].

Baricitinib and ruxolitinib are the only JAK inhibitors being studied in COVID-19 [158,159]. A pilot study with 12 patients treated with baricitinib (BARI-COVID) showed improvement in symptoms and oxygenation compared to the control group, without serious adverse reactions [158]. A study with ruxolitinib was unassociated with accelerated clinical improvement in severe COVID-19 [159].

There are 18 ongoing studies with ruxolitinib and 13 with baricitinib [160]. Possible adverse effects should be considered, and risks versus benefits carefully weighed before considering their use. There is no experience with the use of JAK inhibitors in PLWH infected by COVID-19.

There are no known interactions between baricitinib and cART components. Atazanavir, DRV, cobicistat, ritonavir and lopinavir, which are CYP3A4 inhibitors, may increase the serum concentrations of ruxolitinib, and dose reduction is advisable [154]. There are no data on the doses used for COVID-19.

4.2.3. IL-1 receptor antagonists: anakinra

Anakinra, a recombinant, non-glycosylated IL-1RA (IL-1 receptor antagonist), has been evaluated as a method to counteract the cytokine release observed in severe sepsis and septic shock [161]. Because IL-1 β serum concentrations were significantly increased in COVID-19 patients compared with healthy controls, it is thought that anakinra may block the activity of IL-1 β in these patients [137]. In a retrospective cohort study of patients with COVID-19 and ARDS managed with noninvasive ventilation outside the ICU, treatment with high-dose anakinra was safe and associated with clinical improvement [162]. There are RCT pending results. Limited data are available describing the tolerability and toxicity of high dose anakinra [157]. There is no experience of using anakinra in PLWH infected by COVID-19. No known interaction exists between IL-1 receptor antagonists and cART components.

4.2.4. VEGF inhibitors: bevacizumab

Vascular endothelial growth factor (VEGF) is a potent vascular permeability inducer. Bevacizumab, a recombinant monoclonal antibody that binds to and neutralizes VEGF, was found to inhibit pulmonary edema in a VEGF overexpression model. In comparison to healthy controls, VEGF serum concentrations were significantly increased in patients with COVID-19 [137].

There are 3 RCTs assessing the efficacy and safety of bevacizumab, one of them with recruitment completed [160]. Considerations regarding the risk of serious adverse effects, including myocardial ischemia, cerebral thrombosis, and gastrointestinal perforation, are important in determining whether targeting VEGF is a viable option [163]. There is no known interaction between bevacizumab and cART components.

4.2.5. TNF- α inhibitors: infliximab and adalimumab

TNF- α is a proinflammatory cytokine primarily produced by monocytes and macrophages that induce the production of other cytokines and promote inflammation [164]. The hyper-inflammatory response in COVID-19 is characterized by elevated concentrations of serum TNF-, IL-6, IL-8 and to a lesser

extent IL-1 [9]. Administration of anti-TNF to patients for treatment of autoimmune disease leads to reductions in all these key inflammatory cytokines [165]. This is the rationale that anti-TNF- therapy can decrease inflammation in COVID-19 and have a major impact on the need for ventilation and mortality.

There are a small number of case reports on the use of anti-TNF therapy in acute COVID-19. Currently, there is a clinical trial assessing the efficacy of infliximab in hospitalized adult patients with severe or critical COVID-19 [166].

There is no known interaction between adalimumab and cART components. Co-administration of Infliximab and etravirine may increase the risk of peripheral neuropathy, especially in patients with diabetes or older than 60 years. They should be administered with caution and neurological symptoms monitored. Co-administration of efavirenz with infliximab may potentiate the risk of liver injury. It is recommended to monitor liver function during treatment [107].

(1) Corticosteroids

Systemic corticosteroid treatment is controversial in severe ARDS; however, it is used in patients with severe viral ARDS [167]. Given the large number of cytokines induced by COVID-19 infection, corticosteroids may help to reduce the inflammation that causes lung damage, especially in patients with severe disease [137]. A meta-analysis published in April 2020, in which the studies evaluated were mainly in SARS-CoV and MERS-CoV, and only 2 in SARS-CoV-2, suggested that corticosteroid use is associated with increased mortality in patients with coronavirus pneumonia [168]. Different corticosteroids are currently being evaluated for the treatment of COVID-19. Methylprednisolone and dexamethasone are the most frequently used because of high lung bioavailability.

Limitations of most of the methylprednisolone studies include the small cohort size and the lack of follow-up data, as far as the resolution of lung injury is concerned [169]. Nevertheless, the most robust data came with dexamethasone in the RECOVERY trial [170]. It is the only randomized controlled study, carried out in the UK, where 2104 patients were randomized to dexamethasone 6 mg per day (oral or intravenous) for 10 days and compared to 4321 patients receiving usual care. The trial showed a significant reduction of death by 35% in ventilated patients and by 20% amongst patients on supplemental oxygen therapy, although no benefit was observed in mild cases or moderate cases not requiring oxygen support.

A prospective meta-analysis of clinical trials of critically ill patients with COVID-19 has recently been published [171]. It concludes that administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality. There are few published studies of corticosteroid treatment of COVID-19 infection in PLWH. In the literature, only 21 PLWH with COVID-19 received corticosteroids without assessment on the impact on their outcome [33,41].

Corticosteroids are mainly metabolized by CYP3A4, and therefore their concentrations may increase in the presence of inhibitors such as ritonavir or cobicistat. The cobicistat data

sheet [172] does not recommend co-administration, whereas the ritonavir data sheet [173] recommends avoiding fucicidone, budesonide, or triamcinolone and caution with dexamethasone and prednisolone/prednisone use. Dexamethasone can be used in single doses, but Cushing syndrome has been described in multiple doses, even with eye drops together with RTV-boosted PI. If these associations must be used, careful monitoring of therapeutic effects and adverse reactions is warranted. In the event of glucocorticoid withdrawal, a progressive reduction of the dose may be required over a longer period. Dexamethasone interacts with all PI, not recommended according to the data sheet [174]. High doses of dexamethasone can also decrease plasma concentrations of DRV/c due to CYP3A4 induction with the possible loss of therapeutic effect and induction of resistance. Similarly, it also interacts with elvitegravir. No interactions have been described with dolutegravir and raltegravir. The co-administration of bictegravir and dexamethasone has not been studied. However, caution is required as bictegravir is metabolized by CYP3A4 and UGT1A and co-administration may potentially decrease bictegravir concentration [90]. The use of dexamethasone with rilpivirine is contraindicated [175] because it can significantly decrease plasma concentrations of rilpivirine. It is dose dependent, so a single dose could be used, but long-term use alternatives should be considered. Its use with efavirenz or etravirine is not recommended because of a decrease in antiretroviral drug level. Dexamethasone is a substrate of CYP3A4 and a moderate inducer of CYP3A4 and therefore can decrease doravirine exposure and efficacy [90]. If co-administration cannot be avoided, doravirine should be administered 100 mg twice daily (based on the interaction study with rifabutin, another moderate inducer) and maintained at this dose for at least another two weeks following dexamethasone discontinuation. At least a 4-week cessation period is recommended prior to initiation of doravirine due to the persistent inducing effect upon discontinuation. The same is true for MVC. In contrast, interactions between dexamethasone and NRTI have not been evidenced.

Methylprednisolone is also metabolized by CYP3A4. Co-administration of methylprednisolone with DRV, ritonavir, atazanavir, cobicistat, efavirenz, etravirine or elvitegravir can potentially increase methylprednisolone concentration and increase the risk of steroid side effects [154]. Rilpivirine at a dose of 25 mg once daily is unlikely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes [90]. When the use of corticosteroids is greatly needed, it is recommended to use the lowest possible dose and to monitor the adverse effects together with antiretroviral drug levels [90].

5. Anticoagulant therapy

COVID-19 infection can induce a prothrombotic state, due to the pro-inflammatory state and endothelial dysfunction, with a high risk of arterial and venous thrombosis [176]. The incidence of pulmonary thromboembolism (PTE) in critically ill COVID-19 patients is significantly higher than in patients

with ARDS due to other diseases [177]. Besides, patients who develop a PTE have a worse prognosis [178]. Recent evidence suggests that pulmonary thrombosis originates *in situ*, due to the low incidence of deep vein thrombosis evidenced [179]. Studies indicate that anticoagulant therapy with low molecular weight heparin (LMWH) in patients with severe COVID-19 decreases mortality [180,181]. The latest recommendations suggest that all patients hospitalized should receive thromboprophylaxis or full therapeutic-intensity anticoagulation if such an indication is present [182]. D-dimer could aid in the early recognition of high-risk patients [183]. No interactions have been found between LMWH and cART components.

6. Expert opinion

When two epidemics collide, such as COVID-19 and HIV infection, some questions unavoidably arise. While engrossed by the pandemic, HIV clinicians soon noticed the disproportionately low number of COVID-19 cases amongst PLWH. This finding prompted lucubration about the presumptive protective role of cART on SARS-CoV-2 infection incidence. This speculation was fed by knowledge gathered from the SARS-CoV-1 and MERS-CoV epidemics, showing the sensitivity of these viruses to LPV/r. Given the genetic analogy and the shared pathogenic mechanisms between the three coronaviruses, LPV/r was promoted as a potentially useful therapy for COVID-19. Without question, the colliding epidemics may modify each other, but we do not yet know to what extent the presumed changes will affect PLWH. Nevertheless, what most HIV physicians are currently asking themselves can be summarized in three questions:

1.- Is SARS-CoV-2 infection incidence lower or higher in PLWH?

Current evidence indicates that PLWH have a roughly similar incidence of SARS-CoV-2 infection to the non-HIV-infected population. However, hospitalization rates are lower for PLWH, but information from observational studies in this respect is very biased, since a major problem of this kind of studies is the bias for indication. Therefore, to draw reliable conclusions is difficult. Besides, there is no proof of a protective role of cART or components thereof against the risk of acquiring SARS-CoV-2 infection, despite data from observational studies involving TDF/FTC in such a role. PrEP studies' data may offer a new insight into this issue soon, since evidence from RCT is not expected.

2.- Is COVID-19 severity comparable between PLWH and the uninfected population?

PLWH have a higher prevalence of comorbid conditions associated with a poor prognosis in COVID-19, which may harm all-cause mortality [27]. Lately, data from observational studies suggest higher mortality rates in PLWH after adjusting for age and other confounding factors. Notwithstanding that, other matched studies suggest similar adverse outcomes to those of the uninfected population. Combination antiretroviral therapy does not play a protective role related to COVID-19 outcomes in PLWH.

3.- Shall the management of COVID-19 be different in PLWH?

With the incidence, presentation, and evolving trend of COVID-19 in PLWH being roughly like those of the general population, there are no features for a different management approach in PLWH. Although COVID-19 is a systemic disease,

the main target of SARS-CoV-2 is the lung where acute lung injury, diffuse alveolar damage, and eventually ARDS are the leading causes of death. Why some patients develop acute respiratory failure, while others remain asymptomatic or have minimal symptoms, has not been fully untangled. Severe COVID-19 is frequently associated with ARDS, and since there is no specific pharmacologic therapy for ARDS, painstaking supportive care with the premise of lung-protective ventilation associates with a better outcome. On the other hand, an unequivocal principle in ARDS management is that the treatment of its underlying roots is crucial to upgrade outcomes.

Based on the knowledge gathered about the pathogenesis of COVID-19, combination therapy with antivirals with immunomodulating agents has been proposed. Among the myriad of pharmacological interventions tested during the pandemic's heroic times, only two have shown clinical benefit. RDV is the only antiviral associated with an inconspicuous clinical benefit, since it shortened the time to recovery in hospitalized patients. As of 22 October 2020, the Food and Drug Administration (FDA) has approved Veklury (remdesivir), as the only antiviral drug for the treatment of COVID-19 disease. However, inquiries remain about its efficacy, such as the optimal patient population, the optimal duration of therapy, and the unclear effect on discrete outcomes. In a large open-label and non-randomized clinical trial, dexamethasone decreased the mortality in patients who needed mechanical ventilatory support or had high oxygen therapy requirements. There are limited data, and indeed, not a single RCT to date indicating the presumptive benefit of cytokine or chemokine blockade in COVID-19. Handling a system as intricate, redundant, overlapping, and full of alternate pathways as the immunologic system may prove a massive task for single molecule targeting, and it may sometimes happen to be hazardous. It is worth recollecting that patients who did not need oxygen therapy but received dexamethasone had an excess mortality rate. In addition, corticosteroids inhibit signaling of endogenous type I interferon, a first line of defense against respiratory viral infections.

There is a low number of PLWH with COVID-19 treated, and therefore, no conclusion can be drawn. Hopefully, both RDV and dexamethasone have a good safety profile. However, there is a risk of drug–drug interactions of most antiretroviral drugs with dexamethasone, whereas the likelihood of such an interaction is almost negligible with RDV. The pharmacological management of COVID-19 in PLWH shall not be different from that in the general population except for increased awareness about pharmacokinetic interactions, especially with corticosteroids.

Indeed, for most of the drugs discussed above, there is no evidence from RCT of beneficial effects for COVID-19 patients, either uninfected or PLWH, but with some potentially jeopardizing side effects. In an emergency setting such as that presented by the COVID-19 pandemic, it is useful to recall Milton Friedman's message, 'The power to do good is also the power to harm.'

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PD devised the concept and developed the idea. MMG, IM and GMM performed bibliographic research. All authors coordinated and oversaw the development of the manuscript. All authors participated in data interpretation. The manuscript was drafted by PD. All authors provided input to the report and approved the final version of the manuscript.

Declaration of interest

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