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Raj Patel ORCID iD: 0000-0003-1896-1961

COVID-19 and AIDS: outcomes from the co-existence of two global pandemics and the importance of chronic antiretroviral therapy

Raj H. Patel[1], Arpan Acharya[2], Mahesh Mohan[3] and Siddappa N. Byrareddy[2, 4, 5§]

[1]Edward Via College of Osteopathic Medicine, Monroe, LA, USA.

[2]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Centre, Omaha, NE, USA.

[3]Texas Biomedical Research Institute, Southwest National Primate Research Center, San Antonio, TX 78227, United States.

[4]Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE 68198, USA;

[5]Department of Biochemistry and Molecular Biology, University of Nebraska Medical Centre, Omaha, NE, USA.

[§]**Correspondence:**

Siddappa N. Byrareddy; Associate Professor,

Department of Pharmacology and Experimental Neuroscience,

University of Nebraska Medical Centre, Omaha, NE, USA

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Durham Research Center 8052; 58800 Nebraska Medical Center

Omaha, NE 68198-5880; Phone: +1 402-559-5416

sid.byrareddy@unmc.edu

Abstract

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome 2 (SARS-CoV-2), has created a worldwide pandemic, raising multitude of challenges and uncertainties regarding disease management specific to immunocompromised patient populations. Despite over ~16 million confirmed cases of COVID-19 worldwide as of July 25, 2020, there is a dearth of reports describing the co-infection of Human Immunodeficiency Virus (HIV) and SARS-CoV-2. There are various unknowns regarding the simultaneous impact from these two diseases, despite the fact that the majority of patients with acquired immunodeficiency syndrome (AIDS) are immunocompromised and have comorbidities which can predispose them to severe clinical symptoms, and poorer prognosis, from COVID-19. A large majority of reports indicate that HIV patients with normal CD4 T-cell counts and suppressed viral loads and receiving regular, chronic antiretroviral therapy (cART) do not present with a severe clinical course of COVID-19 and may not be at an increased risk of developing SARS-CoV-2 infection. These favorable indications for HIV patients may be the byproduct of a potential protective factor conferred by antiretroviral therapy which has also been used successfully in previous coronavirus epidemics.

Keywords: AIDS; COVID-19; HIV; SARS-CoV-2; co-infection; cART; antiviral.

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory

syndrome 2 (SARS-CoV-2), has created a worldwide pandemic, raising multitude of challenges and uncertainties regarding disease management specific to immunocompromised patient populations [1]. Despite over ~16 million confirmed cases of COVID-19 worldwide as of July 25, 2020, there is a dearth of reports describing the co-infection of Human Immunodeficiency Virus (HIV) and SARS-CoV-2 [2]. There are various unknowns regarding the simultaneous impact from these two diseases, despite the

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fact that the majority of patients with acquired immunodeficiency syndrome (AIDS) are immunocompromised and have comorbidities which can predispose them to severe clinical symptoms, and poorer prognosis, from COVID-19 [3,4]. A large majority of reports indicate that HIV patients with normal CD4 T-cell counts and suppressed viral loads and receiving regular, chronic antiretroviral therapy (cART) do not present with a severe clinical course of COVID-19 and may not be at an increased risk of developing SARS-CoV-2 infection [5-9]. These favorable indications for HIV patients may be the byproduct of a potential protective factor conferred by antiretroviral therapy which has also been used successfully in previous coronavirus epidemics [10,11].

SARS-CoV-2 and HIV carry numerous similarities as they are both ribonucleic acid (RNA) viruses capable of undergoing mutations and recombination under selection pressure within the host [12]. During the previous SARS-CoV epidemic, the HIV-1 protease inhibitor nelfinavir was found to strongly inhibit the cytopathic effect induced by SARS-CoV infection [10]. Lopinavir was also found to show efficacy both in vivo and in vitro, reducing viral titers and shortening disease progression in case of MERS-CoV infected animals [11]. HIV-1 protease inhibitors including lopinavir/ritonavir and darunavir have been found as efficacious treatment options in patients co-infected with COVID-19 and HIV by reducing SARS-CoV-2 viral loads and accelerating recovery [13-15]. However, recently, remdesivir, a broad-spectrum antiviral drug, has also shown promising results in suppressing SARS-CoV-2 replication in a double-blind, randomized, placebo-controlled trial, where adults hospitalized with COVID-19 that received remdesivir showed reduced respiratory tract involvement [16]. Similarly, tenofovir has also been found to be highly efficacious against SARS-CoV-2 through potently inhibiting

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SARS-CoV-2 RNA dependent RNA polymerase [17]. However, it is important to recognize that clinical evidence regarding the role of antiretroviral therapy, specifically, lopinavir/ritonavir is still emerging. The current COVID-19 treatment guidelines issued by the NIH recommend against the use of lopinavir/ritonavir protease inhibitors (AIII) for the treatment of COVID-19, and is restricted to clinical trials [18,19].

Various large clinical case series have corroborated the growing evidence that patients with HIV/SARS-CoV-2 co-infection do not have excess morbidity and mortality when compared to non-HIV COVID-19 patients. In a study of 47 co-infected patients reported by Gervasoni et al., HIV patients that were hospitalized with SARS-CoV-2 infection generally had favorable outcomes and did not experience severe symptoms requiring intensive care unit admission or mechanical ventilation [9]. Another study by Blanco et al. reporting 5 patients co-infected with HIV/SARS-CoV-2 in Spain, showed that patients who were previously receiving ART prior to admission for COVID-19 experienced less severe symptoms which did not require intensive care unit admission or mechanical ventilation [13]. Härter et al. reported similar outcomes in a study of 33 HIV patients infected with SARS-CoV-2 who were all on antiretroviral therapy at the time of COVID-19 diagnosis [5]. This study also did not support excess mortality and morbidity among HIV patients with COVID-19 when patients were virally suppressed on antiretroviral therapy. Finally, Shalev et al. also reported that HIV patients with COVID-19 shared similar clinical characteristics and outcomes to other hospitalized cohorts in their report of 31 co-infected patients [6]. However, contradictory results have also emerged. Vizcarra et al. report 51 HIV-infected individuals diagnosed with COVID-19 of which six were critically ill and two died [16]. Notably, previous administration of antiretroviral

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therapy, CD4 T-cell counts, CD4/CD8 ratio, and pre-existing comorbidities were not significantly different in recovered patients vs. still-admitted individuals in this study [20]. The authors in this study concluded that HIV-infected individuals should not be considered protected from SARS-CoV-2 or to have lower risk of severe disease. Another study by Suwanwongse et al. reported that 7/9 HIV/SARS-CoV-2 co-infected patients from New York City died from COVID-19 related respiratory failure, despite low HIV viral loads and previous ART regimen [21]. The largest study by Del Amo et al. report 236 HIV/COVID-19 patients from a cohort of 77,590 HIV-positive patients on cART. Out of the 236 patients, 15 were admitted to the ICU, 20 died, and 151 were hospitalized with mild-moderate symptoms [22]. The study notes that HIV-positive patients who received tenofovir/emtricitabine (TDF/FTC) as part of cART regimen were found to have a lower risk for COVID-19 and related hospitalization than those receiving other therapies. This finding conforms with various other molecular docking and case series studies, which demonstrate more favorable outcomes for HIV/COVID-19 patients on tenofovir-based regimens [11,15]. However, this study does not include non-AIDS comorbidities, such as CD4+ T-cell counts, HIV viral RNA loads, and other key confounders, which may influence the results. Further, this study did not report whether or not the patients receiving TDF/FTC had fewer comorbidities than those receiving other forms of ART.

Given the limited available evidence and mixed results from various studies as noted above, it is difficult to draw effective conclusions regarding the outcomes for HIV patients when infected with SARS-CoV-2 at this time and therefore more data/studies are needed to make meaningful conclusions. It is also important to recognize that these

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studies contain limited sample sizes, geographical limitations, and inconsistencies in information, which creates a challenge in stratifying the data to understand the impact of antiretroviral therapy in addition to taking into account individual patient factors and comorbid conditions. Thus, in order to further elucidate the role of cART on SARS-CoV-2, future large cohort studies are warranted with detailed meta-analysis. Nevertheless, these early studies place a spotlight on the unanswered role of antiretroviral therapy in pre-exposure prophylaxis for these patients in preventing incidence of severe clinical symptoms in these patients. Based on the trend of favorable prognosis as seen in the available reports, and the lack of large cohorts of HIV/SARS-CoV-2 infections, it is not unreasonable to believe that HIV patients who have no other comorbidities could be protected from severe COVID-19 clinical symptoms by following a strict chronic antiretroviral regimen.

Further, confounding factors may be present in the form of host factors (immune activation and viral genotypes), which can significantly alter the clinical outcomes in co-infected patients. These factors are often unreported in the majority of studies describing HIV/SARS-CoV-2 co-infection but may still be significant influencers of clinical outcomes. Next, infection with certain HIV subtypes may lead to rapid or slow disease progression, host genetics such as human leukocyte antigen (HLA) can also influence differential clinical outcomes. In regard to immune activation, ART intervention may not completely stop the immune-activation process, and the type of ART may differentially affect immune activation. Thus, depending on the immune activation status of HIV patients co-infected with SARS-CoV-2, a variety of clinical outcomes can be expected, which could partially explain the discrepancies of clinical outcomes among patients with

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HIV/SARS-CoV-2 co-infections in all previously reported studies. Therefore, further large systematic studies are warranted in order to further determine the contribution of these specific genetic/host factors influence the clinical outcomes.

Another possible factor to consider as an explanation for the low incidence of severe outcomes is the impact of social and psychological factors [23]. Are HIV patients following stricter social distancing measures and self-quarantining due to a greater perceived risk of contracting severe SARS-CoV-2 infection? It is also important to consider the backgrounds and demographics of the population represented by HIV patients, which includes drug users, poor patients living in crowded urban slums, migrant workers, sex workers, and prisoners, who may live in environments in which it may be difficult to practice successful social distancing and contact isolation. The challenges of universal HIV testing and now with COVID-19 testing also remains unsolved which can impact the reported incidence and prevalence.

Although more studies are needed, it is undeniable that the overwhelming majority of available evidence regarding HIV/COVID-19 co-infected patients overwhelmingly demonstrates the positive effects of chronic antiretroviral therapy. Individuals who are unaware of their HIV diagnosis and do not have access to antiretroviral therapy may be at heightened risk of experiencing increased morbidity and mortality if infected with SARS-CoV-2. Given the benefits of chronic antiretroviral therapy in reported patients thus far, it becomes increasingly important to sustain the HIV care continuum. Healthcare centers and HIV clinics should work to continue regular follow-up visits for patients and ensure that antiretroviral therapy is adequately rationed for HIV patients and distributed in a timely manner to protect this vulnerable population.

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