

## Hypothetic immunopathological impacts of SARS-CoV-2 and HIV co-infection on COVID-19 severity

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To the Editor,

The world is currently battling against and trying to survive yet another pandemic that threatens human health security. Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), the etiological agent of coronavirus disease 19 (COVID-19), is one of the three most virulent coronaviruses (CoVs). Based on available clinical details, the geriatric group of over 65 years of age and persons with chronic comorbidities such as type-2 diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular diseases, and immunodeficiencies tend to rapidly develop multi-organ failure, severe COVID-19 and ultimately, death.<sup>1</sup> As at 1:10 PM GMT+1, 5<sup>th</sup> May 2020, the global case fatality rate of COVID-19 was approximately 6.9%, whereas 49,623 (2%) of SARS-CoV-2 infected persons were in critical clinical conditions, including acute respiratory distress with or without metabolic acidosis, coagulopathy, and hypoxia.<sup>2</sup>

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Key words: COVID-19; SARS-CoV-2; HIV co-infection; immunopathology.

Contributions: INA conceptualized and designed study; INA, AEA and AUE contributed equally to literature search, drafting the first manuscript, and reviewing for intellectual content. All authors approved the final manuscript before submission.

Received for publication: 15 April 2020.  
Revision received: 5 May 2020.  
Accepted for publication: 15 May 2020.

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Licensee PAGEPress, Italy  
Italian Journal of Medicine 2020; 14:189-191  
doi:10.4081/ijm.2020.1291

To date, very few studies have demonstrated the clinical course of COVID-19 in people living with HIV/AIDS. HIV/AIDS patients are believed to be susceptible to COVID-19, including other opportunistic pathogens due to their compromised immune function. It is assumed that persons who are immunocompromised could have an aggravated pathogenesis of COVID-19 via the activation of chronic inflammatory response.<sup>3</sup> Before the advent of effective highly active antiretroviral therapy (ART), HIV-infected persons with CD4<sup>+</sup> T cell count less than 200 cells/mm<sup>3</sup> were considered to be at high risk of complications associated with respiratory tract infections.<sup>4</sup> Whether this could hold for COVID-19 is yet to be elucidated. It is worthy to note that some persons living with HIV/AIDS and other comorbidities, especially cardiovascular and pulmonary disorders have an increased risk for a more severe course of COVID-19.<sup>5</sup> Thus, additional care for all people living with HIV, especially those with low CD4<sup>+</sup> T cell counts or poorly controlled HIV is necessary. Considering the burden of the global HIV epidemic with a disproportionate concentration in sub-Saharan Africa, Asia and certain parts of Southern Europe, additional preventive measures and management strategies are crucial.<sup>6</sup>

One of the few studies that investigated the clinical interactions of HIV with COVID-19 was that of Guo *et al.*<sup>7</sup> In their study of 1174 HIV infected patients in Wuhan, China 0.68% was confirmed SARS-CoV-2 positive. Importantly, all the HIV-SARS-CoV-2 co-infected patients had HIV load (VL) of <20 copies/ $\mu$ L had relatively adequate CD4<sup>+</sup> T cell counts and clinical symptoms for COVID-19.<sup>7</sup> These indicate that good cellular immunity and low HIV VL could probably facilitate symptomatic COVID-19. Conversely, the study further indicated that HIV/AIDS patients with very low CD4<sup>+</sup> T cell counts were asymptomatic. It could be because several asymptomatic individuals may have missed laboratory testing, even though they were SARS-CoV-2 infected. This supports the hypothesis that immune-compromised HIV/AIDS patients might have some protection from a clinical and severe SARS-CoV attack due to profound anti-inflammatory

response which neutralizes the cytokine storm associated with symptomatic COVID-19.<sup>7</sup> Similar findings that were corroborated by the assertions above are those seen in CD4<sup>+</sup> lymphopenic HIV patient who recovered from SARS-CoV-2 infection.<sup>8</sup>

In another report, 5 out of 543 COVID-19 patients were HIV co-infected in Spain.<sup>9</sup> Four out of the 5 patients had a low HIV viral load (<50 copies /mL). Of these, 2 were on protease-inhibitor-based ART, while the other two were on dolutegravir-based ART.<sup>9</sup> The CD4<sup>+</sup> T cell counts of all those on ART were >400 cells/mm<sup>3</sup>. However, the 5<sup>th</sup> ART-naive patient had a very advanced HIV/AIDS stage with CD4<sup>+</sup> T cell count of 13 cells/mm<sup>3</sup>.<sup>9</sup> Of note, one of the ART experienced, and the ART-naive patients were in severe COVID-19 conditions. As a marker of inflammation, the serum ferritin level of the ART-naive patient was significantly low compared with those on ART. Upon diagnosis, all the 5 patients were immediately placed on anti-SARS-CoV-2 and were switched to boosted-protease inhibitor ART because HIV protease inhibitors may have antagonistic activity against SARS-CoV-2 protease inhibitors.<sup>9</sup> Eventually, the ART-naive alongside 3 of the ART experienced patients were cured of COVID-19. Whereas, one of the initial ART experienced patients with low HIV VL had no sustained SARS-CoV-2 response and remained in intensive care.<sup>9</sup>

Immuno-pathologically, an HIV-associated immunodeficiency leads to cytokine and chemokine dysregulation.<sup>10</sup> Undoubtedly, the host immunologic response is vital for the control and resolution of CoV infections. However, it can also lead to immunopathology, when the immune response is out of control, especially if Th1 and Th17 subsets are activated due to exacerbated immune response.<sup>11</sup> For instance, some plasma cytokines such as tumor necrosis factor- $\alpha$ , interleukins (IL-) 2, 6, and 10 were elevated in COVID-19 patients.<sup>11</sup> Their upregulation culminates in the induction of virus-induced inflammatory storm, one of the major critical conditions experienced by COVID-19 patients.<sup>5</sup> Thus, when individuals living HIV/AIDS eventually get infected with SARS-CoV-2, it is expected they experience synergistic cytokine storm and chronic inflammatory response. In addition, T cell activation and regulation have been shown to increase significantly in COVID-19 patients.<sup>12</sup> In particular, a significant decrease in absolute lymphocyte counts in severe cases of COVID-19 has been reported.<sup>12</sup> CD4<sup>+</sup> and CD8<sup>+</sup> T cells lymphocytopenia were seen primarily in severe cases due to lymphocyte exhaustion.<sup>12</sup> These immunological features could be dangerous for people living with HIV/AIDS, especially the ART-naive ones.

Considering the sustained global rise in the incidence and spread of SARS-CoV-2, there is an urgent need for antiviral drugs that can contain the replication

of both HIV and SARS-CoV-2. For instance, Dolutegravir and Lopinavir/Ritonavir have been recommended by scientists to potentially help to prevent or treat severe COVID-19.<sup>13,14</sup> In addition, remdesivir has been used in many clinical trials to treat COVID-19. Notably, the protease inhibitor, lopinavir/ritonavir, was recommended for the management of COVID-19 based on the experience gained during SARS and MERS epidemics. Recently, the Food and Drug Administration (FDA) of the United States of America issued an emergency approval for the use of remdesivir in the treatment of severe COVID-19.<sup>15</sup>

There is a need for clinicians to carefully evaluate COVID-19 patients for HIV co-infection, especially in high-risk persons such as men who have sex with men (MSM), commercial sex workers, and injection drug users. If found co-infected, these patients should be thoroughly evaluated to determine the most suitable antiviral regimen that could contain both pathogens. In addition, more health education programs that explain the impacts of high-risk activities on HIV and SARS-CoV-2 infections should be implemented.

More studies are needed on the clinical presentations of COVID-19 patients with HIV co-infection, especially from HIV endemic regions, in order to have a better understanding of the immunological and pathological impacts of either pathogen on the other. Finally, it is highly recommended to perform comprehensive evaluation studies on all candidate antiviral agents used in treating HIV/SARS-CoV-2 co-infection in order to assure their potency, efficacy, and safety.

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