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Editorial – Role of Highly Active Antiretroviral Therapy (HAART) for the COVID-19 treatment

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Human immunodeficiency virus (HIV), the worldwide agent of AIDS, counts today 37,9 million cases in the world. The HIV therapy requires multidisciplinary approach due to the possible presence of comorbidities[1-3]. Despite the emergency caused by HIV, in the last year SARS-CoV-2 infection stormed the human population, indeed, 54 million cases of COVID-19 were recorded[4,5].

Due to the high prevalence in the human population of those viruses, the co-infection of SARS-CoV-2 in PLHIV (People Living With HIV) is still a matter of study and debate. Previous studies highlight the appearance of light COVID-19 clinical symptoms in HIV patients.

The current literature debates on the reason why HIV-positive people lack of the major and serious symptoms of COVID-19 if infected by its causative agent, contrary to the general population.

The most accredited theory concerns the use of HAART therapy among HIV patients that could represent a protective factor against SARS-CoV-2. In particular, it is possible that the benefit gained with this therapy have to do with immune reconstitution of the person or with the down modulation of SARS-CoV-2[6].

Nowadays, HIV treatment consists in the HAART (Highly Active Antiretroviral Therapy) therapy that is a combination regimen of, at least, two classes of antiretroviral agents among the five classes available. All these classes are different because they act on distinct steps of the HIV-1 life cycle, generally inhibiting its replication[7,8]. One class, Fusion inhibitors (FIs), binds to the envelope glycoprotein gp41 and prevents viral fusion to the CD4 T-cells such as enfuvirtide[8]. Peptides activity was also demonstrated for similar viruses[10].

The other classes include nucleoside analog reverse transcriptase inhibitor NRTIs (Zidovudine, Lamivudine, Tenofivir, Emtricitabine) and non-nucleoside reverse transcriptase inhibitors NNRTIs (Efavirenz and Nevirapine), both acting on RNA-dependent RNA polymerase (RdRp). The difference between them is that NRTI works as chain terminator so as a competitive substrate, while NNRTI binds RdRp only reducing its activity and definitely acting as a non-competitive inhibitor[7].

The fourth class comprehends agents that inhibit viral DNA insertion into the host cellular genome by specifically inhibiting the viral enzyme integrase INSTIs (Elvitegravir and Raltegravir) and the last one includes protease enzyme inhibitors PIs (Saquinavir, Indinavir, Ritonavir, etc.) which block the viral protease enzyme necessary to assemble the new virus particles[7].

Several papers have reported that drugs belonging to the HAART therapy could also be used for COVID-19 treatment. This, indirectly, underlines the similarity in some mechanisms of action during the life cycle of these two viruses.

It is well established that most of these drugs act on the RNA-dependent RNA polymerase (RdRp). The proof of concept is that the RdRp is highly error-prone, increasing its capacity of accepting modified nucleotide analogues as substrates[11].

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Members of the classes NRTIs and INSTIs as Tenofovir (an acyclic adenosine nucleotide), Lamivudine (a dideoxynucleoside analog RTI), Emtricitabine, Zidovudine (AZT) and Elvitegravir can be all incorporated, terminating nucleotide extension by the RdRP in the polymerase reaction and finally preventing the replication of the virus[11-13].

Moreover, despite the fact that viruses like SARS-CoV-2 mutate rapidly making difficult to establish a specific and appropriate treatment, it has been demonstrated[7] that also its main protease (Mpro) is essential for its life cycle. In this scenario, Efavirenz (a NNRTIs drug) and Raltegravir (an INSTIs drug) have been both tested to conclude that their action on Mpro target stop the replication and proliferation of the virus[14,15].

The window on the HAART therapy reproposing for SARS-CoV-2 treatment is now open. In the meanwhile, Remdesivir (a prodrug of a nucleotide analog that inhibits viral RNA polymerases) is the only drug approved by the FDA (Food and Drug Administration). Other antivirals could be potentially useful but have not yet been shown to be effective[16,17].

Over this year, it has been observed how people already infected by HIV/AIDS answered to SARS-CoV-2 infection. A large number of studies suggest that PLHIV receiving HAART therapy have mild symptoms of COVID-19[18].

By investigating in literature, it turned out that the most interesting drug, between the ones used in HAART therapy, is Tenofivir that other than inhibit RdRp has also shown the ability to diminish the production of some inflammatory molecules that are presented as a storm in some cases of COVID-19 infection[19]. Anyway, whether people with properly controlled HIV are surprisingly protected from the cytokine storm is unknown and worthy of additional study.

To confirm this theory, it has been observed that PLHIV who are not taking HAART increase their risk to contract COVID-19 in a severe form more than the others. Likewise, though we could add that in a period during which physical distancing is required, letting these persons experience a treatment interruption, PLHIV will probably face a major risk to catch COVID-19 once healthcare facilities re-open[20], concluding that we cannot assert with certainty if HAART can prevent the acquisition of COVID-19[21].

To date, even if researches are still ongoing, we could presume that not only HAART therapy is responsible of a less serious evolution of COVID-19 but also a competition mechanism that can be established by these two viruses or even the fact that COVID-19 is serious when a cytokine cascade is triggered, unlike HIV patients, who are immunosuppressed, do not have such inflammatory molecules at their disposal.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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