HIV and SARS-CoV-2: points to consider to face this new pandemic

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Abstract

In December 2019, a new species of pneumonia-causing betacoronavirus was identified in Wuhan, China, which was later identified as SARS-CoV-2. This RNA virus presents certain similarities with other viruses of the same genetic material. It has been seen that infection by human immunodeficiency virus resembles the infection by SARS-CoV-2 in various aspects. In this comment, we present some of the virological, immunological, clinical, and pharmacological similarities between HIV and SARS-CoV-2, which could allow us to understand the immunopathogenesis of COVID-19 better, as well as make some decisions in regarding antiviral management.

Key ideas

- COVID-19 is a systemic disease, with predominantly respiratory clinical manifestations with a strong immunopathogenic basis.
- There is no absolute certainty about the transmission mechanisms of COVID-19, its clinical manifestation, incubation period, or etiologic treatment.
- Its unusual behavior and the fast evolution of the pandemic have necessitated the consideration of new strategies based on previous experiences such as HIV infection, which has some similarities with SARS-CoV-2.
- T cells play a fundamental role in the expression of symptoms and transmissibility. Likewise, some antiretrovirals used in HIV infection may be useful for the treatment of SARS-CoV-2 infection.

Introduction

Since the appearance of SARS-CoV-2 in December 2019, many measures have been taken to contain the transmission of the virus and manage its clinical manifestations. Its unpredictable behavior, and the fast evolution of the pandemic, have forced scientists to consider new strategies. Some strategies are based on previous experiences. HIV infection is one such experience, which showed similarities to the current SARS-CoV-2 infection from a clinical point of view.

Consequently, the present review aims to do an in-depth analysis of these similarities and their mechanisms. Doing so will help us face this pandemic from a different outlook, considering new diagnostic and therapeutic alternatives.

Methods

A PubMed and MEDLINE search was performed with the keywords COVID-19 and HIV, using the Boolean operator "AND" to perform the search as "COVID-19 AND HIV". Once the first search was obtained, the filters "case report," "classical article," "observational study," "review," and "journal article" were applied. Letters to the editor and other forms of publication not included in the search were excluded. At the same time, four articles that were not within the search criteria were selected, which were directly searched to contextualize the disease.

Results

From the initial, unfiltered search (COVID-19 AND HIV), a total of 413 articles were obtained. After applying the filters, 271 articles were obtained, of which 17 articles that dealt with the association between COVID-19 and HIV were selected for the present review.

Also, four directed articles were used in order to contextualize the disease.

Coronavirus disease 2019 (COVID-19)

Coronaviruses (CoVs) are enveloped viruses of positive polarity single-stranded ribonucleic acid (Baltimore group IV) with a genome of 26 to 32 kilobases, belonging to the *Coronaviridae* family and *Coronavirinae* subfamily, of which there are four main genera, alphacoronavirus, betacoronavirus, deltacoronavirus, and gammacoronavirus[1].

CoVs have been identified in various avian hosts and mammals, including camels, bats, mice, dogs, and cats[1].

In December 2019, Zhu et al.[2] described in the Chinese city of Wuhan, a new coronavirus that caused pneumonia, which would later be called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes the coronavirus disease 2019 (COVID-19).

The rapid distribution of the virus in the world, as well as its high contagion rate, have drawn attention since its inception, a situation that leaves us in a position in which we do not have absolute certainty about the transmission mechanisms, clinical manifestations, incubation period, or its etiological treatment.

COVID-19 is a systemic disease, with predominantly respiratory clinical manifestations caused by the SARS-CoV-2 virus[3].

COVID-19 and HIV

Virological aspects

HIV is a member of the genus Lentivirus, which is part of the *Retroviridae* family. Its genetic material is composed of ribonucleic acid, which, through the action of reverse transcriptase, is transformed into deoxyribonucleic acid for its subsequent translation and integration into the host genome[4]. For its part, SARS-CoV-2 is a single-stranded ribonucleic acid virus with positive polarity (Baltimore group IV) belonging to the *Coronaviridae* family, *Coronavirinae* subfamily, and Betacoronavirus genus[1].

Thus, the main similarity between the two viruses is in their genetic material as ribonucleic acid viruses. This is important since the nature of viral ribonucleic acid polymerases confers an evolutionary advantage over other viruses, allowing fast adaptation in the face of new environmental conditions[5]. Other ribonucleic acid viruses with pandemic potential that have been identified are Influenza, Ebola, Nipah, Hendra, SARS-CoV, and MERS-CoV[5].

The life cycle of SARS-CoV-2 consists of five main steps: union, penetration, biosynthesis, maturation, and release. SARS-CoV-2 binds to the host cell by interacting with the viral spike protein (S) with angiotensin-converting enzyme 2 receptors present in the lungs, heart, ileum, kidneys, and bladder. In the lungs, angiotensin-converting enzyme 2 receptor is expressed mainly in lung epithelial cells[5].

Immunological aspects

The angiotensin-converting enzyme 2 receptor is highly expressed in the apical portion of pulmonary epithelial cells in the alveolar space, in which the virus can enter and destroy them. Epithelial cells, alveolar macrophages, and dendritic cells are the main components of innate airway immunity.

Dendritic cells and macrophages work by fighting the virus as innate immune cells until adaptive immunity is involved.

SARS-CoV-2 can bind to dendritic cells through DC-SIGN (dendritic-cell specific intercellular adhesion molecule-3-grabbing nonintegrin), a molecule highly expressed in dendritic cells and macrophages. Once SARS-CoV-2 is bound by dendritic-cell specific intercellular adhesion molecule-3-grabbing nonintegrin to dendritic cells and macrophages, it is transported through the lymphatic system to the lymph nodes. Once there, antigen-presenting cells present viral antigens to T cells, with subpopulations playing an important role. CD4+ and CD8+[6].

For its part, HIV can enter the body free virus or within infected cells. Days after contagion, it is already possible to find HIV in regional lymph nodes. These reach the lymph nodes transported by the dendritic cells of the mucosa via afferent[4]. Dendritic cell-mediated transport of HIV is mediated by the expression of dendritic-cell specific intercellular adhesion molecule-3-grabbing nonintegrin, a molecule that allows these cells to capture HIV, taking it to lymphoid tissue[7].

One of the most striking events in COVID-19, as in HIV infection, is early-stage lymphopenia. One of the hypotheses that have been raised is the generation of a process called lymphocyte depletion, which consists of a worsening of the T cell function, which expresses transcriptional regulators such as FOXP3 and BLIMP-1. This process has also been observed in other viral infections, such as HIV infection[8]. CD4+ T cells show increased expression of TIGIT, Tim-3, whereas CD8+ T cells increase expression of PD-1 and NKG2A[8].

The expression of these regulatory factors causes a functional deterioration of CD4+ T, CD8+ T, and NK cells and a decrease in the number of CD8+ T cells.

On the other hand, recent evidence suggests that in the subgroup of severe COVID-19 patients, who present with cytokine storm, hemophagocytic lymphohistiocytosis may occur secondarily.

Therefore, SARS-CoV-2 would produce an inactivation of antiviral immunity in the disease's primary stage, mediated by two important immunopathogenic events. On the one hand, the functional depletion of T cells and, on the other hand, the production of a cytokine release syndrome with hemophagocytic lymphohistiocytosis, which leads to functional dysfunction and decreased numbers of T cells, respectively[8].

Clinical aspects

Regarding clinical manifestations, primary HIV infection is usually associated with a clinical picture known as acute retroviral syndrome, characterized by fever, generalized lymphadenopathy, myalgias, general malaise, cough, odynophagia, and nonspecific rash—symptoms generally known as "influenza type" or "flu-like." These manifestations are directly related to the increase in viral load[4,7].

For its part, COVID-19, especially in patients with moderate to severe disease, usually presents initially with cough, fever, myalgias, headache, and dyspnea. Manifestations are conditioned with the high viral load in the initial stages[9].

Therefore, both diseases have common manifestations of "influenza-like" disease directly associated with an increase in viremia.

Outcomes in people living with HIV and COVID-19

Although there is a tendency to think that those living with HIV have a higher risk of severe COVID-19 and mortality, several studies have shown no increased risk of severe disease or increased mortality in HIV-positive individuals.

In a study published by Sigel et al., no differences were found in adverse outcomes in hospitalized HIV-positive individuals compared to a demographically similar group. There were no differences in severity at hospital admission ($p = 0.15$), and the cumulative incidence of death was similar over time ($p = 0.94$)[10]. Similarly, Gudipati et al. concluded in a descriptive study that PLHIV does not have an increased risk of severe illness or death than patients who are not living with HIV[11].

While it is striking that people living with HIV are not at increased risk of severe illness or death, Vizcarra et al. concluded in a prospective single-center cohort study that people living with HIV should not be considered protected from SARS-CoV-2 infection[12].

Pharmacological aspects

One of the first strategies to treat SARS-CoV-2 infection was the use of drugs used to treat HIV, such as the protease inhibitor lopinavir boosted with ritonavir; however, no benefit was observed in its use compared with standard care[13]. Later the tests with other pharmacological groups such as nucleotide analogs showed better activity against SARS-CoV-2. This is the case with remdesivir, which is superior to placebo in shortening the recovery time in adults hospitalized for COVID-19[14]. On the other hand, it has been seen that in people living with HIV, the use of nucleotide analogs such as tenofovir with emtricitabine provides a lower risk of COVID-19[15]. Some molecular docking studies suggest using nucleotide analogs such as tenofovir disoproxil fumarate, tenofovir alafenamide, abacavir, and lamivudine, may be effective against SARS-CoV-2 by inhibiting ribonucleic acid polymerase dependent on ribonucleic acid[16,17].

Discussions

There are many similarities between SARS-CoV-2 and HIV. The similarities in the use of ribonucleic acid polymerases are striking, which could explain why the assays with nucleotide analogs have yielded promising results, and protease inhibitors have not.

On the other hand, dendritic cells and T cells play a fundamental role in both diseases' immunopathogenesis. First, virus transport mechanisms mediated by dendritic-cell specific intercellular adhesion molecule-3-grabbing nonintegrin are very similar between SARS-CoV-2 and HIV. Second, the lymphocyte dysfunction present in both infections could partly explain why patients with SARS-CoV-2 coinfection and HIV do not have worse outcomes than those who do not live with HIV.

Similarly, the process of binding to the cell and fusion of the virion with the membrane could shed light on new pharmacological targets.

COVID-19 has to be viewed globally with the same perspective as HIV, as this may be the way to obtain answers to our possible containment and management plans for the disease..

Conclusions

SARS-CoV-2 and HIV have multiple similarities. Regarding the virological aspects, the composition of the genetic material of both viruses stands out. Ribonucleic acid stands out, which is not insignificant since replacing their genetic material requires ribonucleic acid polymerases, which give these viruses an evolutionary advantage and making them adapt better to changes in the environment.

Immunological aspects are undoubtedly the cornerstone of both SARS-CoV-2 and HIV infection, where T-cell dysfunction, either due to decreased numbers or functional exhaustion, seems to play an essential role in the immunopathogenesis of both diseases. The expression of regulatory factors such as FOXP3 and BLIMP-1 in T cells, as well as an increase in the expression of TIGIT and Tim-3 in CD4+ T cells together with PD-1 and NKG2A in CD8+ T cells, are markers of lymphocyte depletion, a process that has been seen in both HIV and SARS-CoV-2 infection.

Regarding the disease's initial presentation, both the acute retroviral syndrome due to HIV and COVID-19 present lymphopenia. It is associated with a high viral load in the blood, both with "flu-like" symptoms.

The outcomes are for clinicians, one of the most relevant elements when studying the disease. Several studies concluded that SARS-CoV-2 and HIV coinfection is not associated with an increased risk of serious illness or death compared to SARS-CoV-2 infected people who do not live with HIV.

Regarding management, remdesivir has been the only antiviral drug that alone has been shown to shorten the recovery time in adults hospitalized for COVID-19 to date. This opens the door to consider the possibility of testing with other drugs of the same family (nucleotide analogs), especially those used for HIV infection such as TDF, TAF, ABC, and 3TC, as some molecular docking studies have suggested that these drugs may be effective in inhibiting ribonucleic acid-dependent ribonucleic acid polymerase.

Notes

Authorship roles

APP: conceptualization, methodology, research, resources, writing the manuscript (preparation), visualization, and administration of the project. FSS: conceptualization, resources, writing of the manuscript (revision), visualization, and supervision.

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Conflict of interests
The authors declare that they have no conflicts of interest with the subject of this article.

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Ethical considerations
In the present study, an analysis of secondary data was carried out, obtained from a public access information source on the PubMed / MEDLINE platform.

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References

1. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Feb 22;395(10224):565-574. | CrossRef | PubMed |
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727-733. | CrossRef | PubMed |
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. | CrossRef | PubMed |
4. Deeks SG, Overbaugh J, Phillips A, Buchbinder S. HIV infection. Nat Rev Dis Primers. 2015 Oct 1;1:15035. | CrossRef | PubMed |
5. Soriano V, Barreiro P, Ramos JM, Eirós JM, de Mendoza C. COVID-19 Comes 40 Years After AIDS - Any Lesson? AIDS Rev. 2020 Jul 8;22(2):63-77. | CrossRef | PubMed |
6. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020 Jun;215:108427. | CrossRef | PubMed |
7. Sepúlveda C, Afani A. SIDA. 4a Ed. Santiago de Chile: Mediterráneo; 2009.
8. Fathi N, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. Cell Biol Int. 2020 Sep;44(9):1792-1797. | CrossRef | PubMed |
9. Departamento de Epidemiología. Informe Epidemiológico N°40 Enfermedad por SARS-CoV-2 (COVID-19) Chile 07-08-2020. Santiago de Chile: Ministerio de Salud; 2020. [On line]. | Link |
10. Sigel K, Swartz T, Golden E, Paranjpe I, Somani S, Richter F, et al. Covid-19 and People with HIV Infection: Outcomes for Hospitalized Patients in New York City. Clin Infect Dis. 2020 Jun 28:ciaa880. | CrossRef | PubMed |
11. Gudipati S, Brar I, Murray S, McKinnon JE, Yared N, Markowitz N. Descriptive Analysis of Patients Living With HIV Affected by COVID-19. J Acquir Immune Defic Syndr. 2020 Oct 1;85(2):123-126. | CrossRef | PubMed |
12. Vizcarra P, Pérez-Elías MJ, Quereda C, Moreno A, Vivancos MJ, Dronda F, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. Lancet HIV. 2020 Aug;7(8):e554-e564. | CrossRef | PubMed |
13. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 May 7;382(19):1787-1799. | CrossRef | PubMed |
14. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020 Oct 8:NEJMoa2007764. | CrossRef | PubMed |
15. Del Amo J, Polo R, Moreno S, Díaz A, Martínez E, Arribas JR, et al. Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy : A Cohort Study. Ann Intern Med. 2020 Oct 6;173(7):536-541. | CrossRef | PubMed |
16. Chien M, Anderson TK, Jockusch S, Tao C, Kumar S, Li X, et al. Nucleotide Analogues as Inhibitors of SARS-CoV-2 Polymerase. bioRxiv [Preprint]. 2020 Mar 20:2020.03.18.997585. | CrossRef | PubMed |
17. Cottrell ML, Garrett KL, Prince HMA, Sykes C, Schauer A, Emerson CW, et al. Single-dose pharmacokinetics of tenofovir alafenamide and its active metabolite in the mucosal tissues. J Antimicrob Chemother. 2017 Jun 1;72(6):1731-1740. | CrossRef | PubMed |

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