



## COMPARATIVE ANALYSIS OF PANDEMICS HIV/AIDS AND COVID-19

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### ABSTRACT

During recent four decades, the world has faced two horrific, deadly pandemics. In the background of the ongoing pandemic HIV/AIDS, the people were affected with the newly emerging Corona virus SARS-CoV-2, that rapidly turned into pandemic dimensions. There are data that, in various aspects, HIV infection was similar to SARS-CoV-2. The purpose of this review was to search for similarities and differences between both pandemics in view to use the experience of the past and knowledge we have acquired in order to better overcome current and future pandemics.

**Material/Methods:** The literature used is based on databases PubMed, Embase and random search on the Internet with the keywords COVID-19 and HIV, as well the Boolean operator “AND” to achieve a search of “COVID-19 and HIV”.

**Review Results:** In the present review summary, we provide data for similarities and differences regarding virological, immunologic, clinical and pharmacological aspects of HIV and SARS-CoV-2 infections and associated with them pandemics.

**Conclusion:** SARS-CoV-2 was here and will remain here. COVID-19 is not the last pandemic, and people should be prepared for new encounters with agents of high virulence and pandemic potential.

**Keywords:** pandemics, COVID-19, HIV/AIDS, similarities, differences,

### BACKGROUND

During the last 40 years, the world has experienced two horrific pandemics that have dramatically changed our life-style. In addition to the ongoing HIV/AIDS pandemic, the world has faced the threat of a newly emerging coronavirus, SARS-CoV-2. The unusual, unpredictable behaviour of SARS-CoV-2 and its rapid spread necessitated an urgent search for transmission containment strategies and therapies based on previous experience gained from the HIV pandemic. The COVID-19 pandemic resembles HIV/AIDS in various aspects, but despite the similarities, there are important differences.

The **aim** of this article is to find similarities and differences between the two pandemics, with a view to using the experience of the past, the knowledge we already have to better deal with the current and future pandemics.

### METHODS

A literature search was conducted in the databases PubMed, Embase, and a free Internet search, using the keywords COVID-19 and HIV, as well as the Boolean operator “AND” to implement a search for “COVID-19 and HIV”.

### REVIEW RESULTS

In this review article, we present data on similarities and differences regarding virological, immunological, clinical, and pharmacological aspects of HIV and SARS-CoV-2 infections and their associated pandemics.

#### *Morphology of the viruses.*

HIV is an RNA virus, genus Lentivirus, family Retroviridae. After infection of the target cell, the viral RNA, under the action of the enzyme reverse transcriptase, is transformed into DNA for subsequent translation and integration into the host genome. Lentiviruses have a long latency period and can cause chronic and deadly diseases.

SARS-CoV-2 is a member of the large family Coronaviridae, which includes 7 representatives pathogenic to humans. Coronaviruses are 60-140 nm in diameter, enveloped and single-stranded RNA, with the largest genome among RNA viruses. SARS-CoV-2 is a  $\beta$  coronavirus.

### ***Mode of infection:***

A person can become infected with HIV through direct contact with bodily fluids that contain the virus: blood, sexual fluids and breast milk. Risk factors for HIV transmission include unprotected sex, sharing needles and/or syringes, and mother-to-child transmission (transplacental, perinatal, or breast milk). Persons with an undetectable viral load have a minimal risk of HIV transmission by sexual and vertical mechanisms [1, 2, 3].

A significant difference is that SARS-CoV-2 is very easily transmitted by the airborne route via respiratory droplets when coughing, sneezing or talking, and in some cases, contaminated surfaces. It does not integrate into the genome of the infected cell [4]. Antibody generation 15 days after infection is 100% in both mild and severe cases.

### ***Similarities between the viruses.***

The main similarity is in their genetic material - RNA. Viral RNA polymerases make "mistakes" in replication with the appearance of new mutations, which provides an evolutionary advantage - rapid adaptation to new environmental conditions [5, 6]. Other RNA viruses with pandemic potential have been identified: influenza, Ebola, Nipah, Hendra, SARS-CoV, and MERS-CoV [5, 7].

HIV and SARS-CoV-2 are viruses of animal origin and have crossed into the human population from infected animals (monkeys for HIV and bats for SARS-CoV-2).

### ***Differences between the viruses.***

A significant difference is that SARS-CoV-2 is very easily transmitted than HIV.

### ***Similarities between pandemics***

At their onset, both pandemics caused fear and horror because of the gross disruption of the way of life and the death of many people. During the first period of total shock, the world reacted with denial, neglect and delayed adequate response. Viruses were new, there had no known effective antiviral agents, necessitating the approbation of drugs for other diseases. In COVID-19, there were additional factors – the disease is more contagious than expected, can seriously affect young individuals without comorbidities, proceeds with respiratory failure, requires prolonged hospitalization, and rapidly leads to the death of many people. Panic was exacerbated by the presence of the Internet, information overload, the spread of unfounded rumours and hyperconnectivity in our current lives [6,7]. Another similarity is the need for discipline and adherence to health recommendations and protocols by the whole society, which proves to be a difficult task.

### ***Differences between pandemics.***

An important difference between the pandemics is their timelines, the dynamics of their spread. HIV infections within 40 years have been 78 million, 39 million have died, and there are currently 37.7 million people living with HIV (PLHIV). HIV remains a global public health problem with a relatively slow spread. Within two years, confirmed COVID-19 cases were 504.5 million, with 6.2 - 12 million deaths [2, 3].

### ***Contagiousness.***

HIV-infected individuals are most contagious during the acute phase and remain infectious for life if they do not receive treatment (6). COVID-19 patients are contagious for about 10 days. The easy mechanism of transmission, the high reproductive number, and the possibility that SARS-CoV-2 can also be transmitted by people with no or mild symptoms may explain the sudden pandemic spread of COVID-19 [8].

### ***Lethality.***

HIV attacks a person's immune system, rendering them defenseless and unable to fight off a number of diseases. Without treatment, HIV infection progresses to the final phase – AIDS with total immune collapse, development of opportunistic infections, neoplasms, neurological damage and death in 95% of cases. The lethality rate in COVID-19 is 5 - 6% in the untreated, although it reaches 49% in certain population groups.

### ***HIV and SARS-CoV-2 life cycle.***

The SARS-CoV-2 life cycle includes five major steps: fusion, entry, biosynthesis, maturation and release. SARS-CoV-2 binds to the host cell by the interaction of the viral spike protein (S) with angiotensin-converting enzyme 2 (ACE 2) receptors. It is expressed in the lung, small intestine, endothelial and smooth muscle cells of almost all organs. In the lungs, the ACE 2 receptor is expressed mainly in lung epithelial cells, type 2 pneumocytes. Like HIV gp120, SARS-CoV-2 S protein recognizes cell surface receptors, allowing it to enter cells; the difference is in the specific receptors and target cells – SARS-CoV2 binds to ACE2 and enters mucosal epithelial cells, whereas HIV binds to the cluster of differentiation 4 (CD4) receptor and enters CD4+ T cells [2, 9].

### ***Immunological aspects.***

The main components of innate airway immunity encountered by SARS-CoV-2 are epithelial cells, alveolar macrophages (Ma) and dendritic cells (DC). DC and Ma fight the virus until adaptive immunity is activated. SARS-CoV-2 can bind to DCs and Ma via DC-SIGN (specific intercellular adhesion molecule) highly expressed on their surface. DC and Ma transport the virus to the lymph nodes, where antigen-presenting cells present viral antigens to T cells [1, 3, 10]. In HIV infection, the first cells encountered by the virus are also DCs. HIV transport is mediated by the expression of the DC-SIGN molecule (dendritic cell-specific intercellular adhesion molecule-3-not linked to integrin), which allows these cells to capture HIV, transporting it into the lymphoid tissue. Days after infection, HIV can be detected in regional lymph nodes. Dendritic cells and T cells play a major role in the immunopathogenesis of both diseases. The viral transport mechanisms mediated by the DC-specific intercellular adhesion molecule-3-associated no integrin are very similar between SARS CoV-2 and HIV [10].

### ***Pathogenesis.***

SARS-CoV-2 and HIV have induced cytokine storm. Many viral infections cause a hyperinflammatory syndrome that leads to cytopenia, fever, and pulmonary

involvement (including acute respiratory distress syndrome (ARDS) in about half of patients [11]. Cytokine storm is typically characterized by a decrease in inhibitory cytokines (IL-10, TGF- $\beta$ ), an increase in activating cytokines (IL-12, IFN- $\gamma$ , TNF- $\alpha$ ), and increased leukocyte infiltration into inflammatory foci [10, 11]. In most cases, HIV infection induces an inflammatory response that manifests as acute retroviral syndrome, or acute HIV infection (AHI). AHI is usually self-limiting but can lead to a sudden and severe inflammatory process similar to the “cytokine storm” syndrome [11]. Increases in certain plasma cytokines and chemokines occur very early after infection, and cytokine storm is associated with AHI in the period with peak viremia [11]. Importantly, the cytokine storm in HIV infection subsides without therapy but is incomplete; some cytokines remain at levels higher than normal and persist into the chronic phase [1, 2, 3]. Severe clinical forms of COVID-19 are associated with a hyper-immune response. Studies have shown that mortality in COVID-19 is primarily associated with virus-induced hyperinflammation, likely caused by a cytokine storm [11, 12]. The overproduction of proinflammatory cytokines (TNF, IL-6, and IL-1 $\beta$ ) is an early response in this cytokine storm. This potentially leads to an increased risk of vascular hyperpermeability, multiorgan failure, and, ultimately, death when high cytokine levels are not controlled. Both viruses generate increased cytokine production, which is associated with viral load, and cytokines are associated with secondary complications. It is well known that cytokine release in HIV infection is a chronic mechanism associated with chronic inflammation. Prolonged inflammatory status is associated with increased intestinal permeability and bacterial translocation in PLWH. Intestinal permeability, bacterial translocation, or systemic inflammation cannot be abolished with antiretroviral therapy [2, 3]. Residual viral replication and other co-infections also contribute to prolonged inflammatory status. Serum levels of proinflammatory IL-6 are independently associated with morbidity (cardiovascular disease, cancer, etc.) and mortality in replication-controlled VZV. Regarding COVID-19, cytokine secretion is an acute response and is associated with clinical manifestations. Proinflammatory cytokines and chemokines attract more inflammatory cells to migrate from the blood, enhancing tissue destruction. Cytokine storm is responsible for acute respiratory distress syndrome and/or polyorgan dysfunction [11, 12].

#### ***Clinical aspects.***

Incubation period. The incubation period is 5 days (2-14) for COVID-19 and 2-4 weeks for HIV. In terms of clinical features, AHI manifests with a clinical picture of ‘influenza-like’ or ‘flu-like syndrome’ (high fever, generalized lymphadenopathy, myalgias, general malaise, cough, odynophagia and non-specific rash. These manifestations are directly related to the high viral load.

On the other hand, COVID-19, especially in patients with moderate to severe disease, usually initially manifests with cough, fever, myalgias, headache, and

dyspnea. The manifestations are conditioned by the high viral load in the initial stages. Therefore, both diseases have initial manifestations of “influenza-like” illness directly associated with high and increasing viremia [12, 13]. Lymphopenia is among the most prominent features of SARS-CoV-2 and HIV infection. One hypothesis under discussion is the generation of a process called lymphocyte depletion, an impairment in the function of T cells that express transcriptional regulators such as FOXP3 and BLIMP-1. This process has also been observed in HIV infection. CD4+ T cells show increased expression of TIGIT, Tim-3 and CD8+ T cells show increased expression of PD1 and NKG2A. Expression of these regulatory factors leads to impaired CD4+ T<sub>H</sub>1, CD8+ T<sub>H</sub>1 and NK cell function [7, 8, 12, 14,]. On the other hand, there is evidence that in patients with severe COVID-19 and cytokine storm, hemophagocytic lymphohistiocytosis may secondarily occur. Therefore, SARS-CoV-2 can induce inhibition of antiviral immunity in the early stage of the disease through two important immunopathogenetic events: (1) functional depletion of T cells and (2) cytokine release syndrome inducing hemophagocytic lymphohistiocytosis, resulting in functional dysfunction and consequently reduced T cell numbers.

Worldwide, 75% of PLHIV receive antiretroviral therapy (ART) in therapeutic regimens including  $\geq 2$  ARVs that suppress viral replication to the point of undetectable viral load, prevent progression of infection, transmission, and provide prolonged survival and high quality of life (HR)QL.

Antiviral agents proven effective in COVID-19 include Remdesivir (Veklury), Paxlovid (Nirmatrelvir/r); Molnupiravir and monoclonal antibodies (Bebtelovimab) [15, 16, 17, 21].

#### ***Prophylactics.***

Public Health was largely able to contain COVID-19 within a few months through isolation, testing, contact tracing and strict health measures. SARS-CoV-2 proved to be an immunologically favorable and accessible target, and vaccines were created in an unprecedentedly short time frame. Safe and effective vaccines are available that can reduce transmission and severity of symptoms to prevent a person from becoming seriously ill if COVID-19 develops [19]. The introduction of COVID-19 vaccines continues worldwide with the goal of achieving collective immunity as soon as possible. Scientists continue their research to develop new and more effective vaccines. Public health measures differ with respect to prevention for HIV and SARS-CoV-2. There are currently no vaccines for HIV, but there are treatment options, PrEP, PEP, that can help control infection [2, 3, 19, 20].

About HIV there are problems in creating an HIV vaccine. HIV has proven to be the most challenging vaccine target known to date. The reasons are complex and include: active, rapid “error-prone” replication processes; extreme variability with the presence of many viral mutants and sequence diversity. Once HIV infects a cell, it maintains a persistent infection for life. No examples of

natural clearance and no “natural immunity”. HIV evades, eludes the antiviral humoral and cell-mediated immune response.

#### **Latency.**

The early formation of latent HIV reservoirs is well known. Immune correlates of protection still remain unclear. The use of attenuated HIV is unsafe for human use. Work is underway to develop broadly neutralizing antibodies (bNabs) that are capable of stopping a wide range of HIV strains, but there is as yet no method to induce their production.

#### **CONCLUSION**

Surveys concerning vaccines for HIV-1 enabled unprecedentedly rapid progress to produce COVID-19 vaccines and verification of their efficiency. It is an indication that: (1) the control of epidemic could be a success and funding of surveys could be found within a frame of some months; (2) public institutions, universities, non-profit pharmaceutical companies and organizations could and should work together to create life-preserving and life-extending technologies. The gap in vaccine access for low- and middle-income countries must be addressed to achieve high immunization coverage. Key lessons from the HIV/AIDS pandemic that are useful in planning and implementing responses to COVID-19 and future pandemics include: Maintaining a strong and stable health system with a focus on human resources. Ensure sufficient investment to strengthen research and innovation with a focus on the development of new medicines, vaccines and diagnostics. COVID-19 is an opportunity to turn the current crisis into a turning point towards creating a strong, healthy and reliable health system.

#### **Abbreviations:**

**HIV** - Human immunodeficiency virus,  
**AIDS** - Acquired immunodeficiency syndrome,  
**COVID-19** - Coronavirus disease 2019,  
**SARS-CoV-2** - Severe acute respiratory syndrome coronavirus 2,  
**RNA** - Ribonucleic acid,  
**MERS-CoV** - Middle East respiratory syndrome-related coronavirus,  
**PLHIV** - People Living With HIV,  
**ACE 2** - angiotensin-converting enzyme 2,  
**Ma** - macrophages,  
**DC** - dendritic cells,  
**DC-SIGN molecule** - dendritic cell-specific intercellular adhesion molecule,  
**ARDS** - acute respiratory distress syndrome,  
**IL-12** - interleukin 12,  
**IFN- $\gamma$**  - interferon-gamma,  
**TNF- $\alpha$**  - tumor necrosis factor-alpha,  
**VZV** - Varicella zoster virus,  
**FOXP3** - protein involved in immune system responses,  
**BLIMP-1** - B lymphocyte-induced maturation protein-1,  
**PD-1** - programmed death,  
**NKG2A** - Natural killer cells G2A,  
**TIGIT** - T cell immunoreceptor with Ig,  
**ART** - antiretroviral therapy,  
**PrEP-Pre** - exposure prophylaxis,  
**PEP-Post** - exposure prophylaxis

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