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Review

Emergence and molecular mechanisms of SARS-CoV-2 and HIV to target host cells and potential therapeutics

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ABSTRACT

The emergence of a new coronavirus, in around late December 2019 which had first been reported in Wuhan, China has now developed into a massive threat to global public health. The World Health Organization (WHO) has named the disease caused by the virus as COVID-19 and the virus which is the culprit was renamed from the initial novel respiratory 2019 coronavirus to SARS-CoV-2. The person-to-person transmission of this virus is ongoing despite drastic public health mitigation measures such as social distancing and movement restrictions implemented in most countries. Understanding the source of such an infectious pathogen is crucial to develop a means of avoiding transmission and further to develop therapeutic drugs and vaccines. To identify the etiological source of a novel human pathogen is a dynamic process that needs comprehensive and extensive scientific validations, such as observed in the Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and human immunodeficiency virus (HIV) cases. In this context, this review is devoted to understanding the taxonomic characteristics of SARS-CoV-2 and HIV. Herein, we discuss the emergence and molecular mechanisms of both viral infections. Nevertheless, no vaccine or therapeutic drug is yet to be approved for the treatment of SARS-CoV-2, although it is highly likely that new effective medications that target the virus specifically will take years to establish. Therefore, this review reflects the latest repurpose of existing antiviral therapeutic drug choices available to combat SARS-CoV-2.

List of abbreviation

CoVs	Coronaviruses
CNS	Central nervous system
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
MERS-CoV	Middle East respiratory syndrome coronavirus
ARDS	Acute respiratory distress syndrome
WHO	World Health Organization
HIVs	Human immunodeficiency viruses
SIV	Immunodeficiency virus
GP41	Glycoprotein-41
CCR5	C-C chemokine receptor-5
CXCR4	C-C chemokine receptor-4
(IFI)-16	Interferon-gamma induced protein-16
IL-1β	Interleukin-1β
ACE2	Angiotensin-converting enzyme-2
FGF2	Basic fibroblast growth factor 2
GCSF	Granulocyte-colony stimulating factor
IFNγ	Interferon-gamma
IP10	IFN-γ-inducible protein-10
MCP1	Monocyte chemoattractant protein 1
MIP1A	Macrophage inflammatory proteins
TNF-α	Tumor necrosis factor-alpha
TGF-β	Transforming growth factor-beta
NCBD	National Center for Biotechnology Development
FDA	Food and Drug Administration
LPV	Lopinavir
RTV	Ritonavir
PWH	People with HIV

1. Introduction

Coronaviruses (CoVs) are a group of enveloped and positive single-stranded RNA genome viruses that infect both animals and humans (Smith and Denison, 2013; Xu et al., 2020). They contain the largest known RNA genomes ranging from 27 to 32 kilobases in length (Smith and Denison, 2013). Coronavirus-related infections are known to affect

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the liver, central nervous system (CNS), respiratory and gastrointestinal tract of various birds and mammals, including humans (Xu et al., 2020). They are classified into four genera: *Alphacoronavirus, Betacoronavirus, Gammacoronavirus,* and *Deltacoronavirus* (Fung et al., 2020). The novel 2019 coronavirus (2019-nCoV) also belongs to the same group of CoVs. It was named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) (Fung et al., 2020). The transmission pattern of SARS-CoV-2 primarily involves direct close contact with the infected person via nose and mouth secretions, however it can also be transmitted indirectly through contaminated objects or surfaces (World Health Organization). It was discovered in late December 2019 in Wuhan city of China in patients with acute respiratory distress syndrome (ARDS) symptoms, such as fever, cough, and dyspnea (Q.Li et al., 2020b; F.Zhu et al., 2020a) after isolated from the respiratory epithelium (Xu et al., 2020). The genome sequence analysis of SARS-CoV-2 showed that it belongs to the *Betacoronavirus* genus (β-CoV) (Lu et al., 2020b). The SARS-CoV-2-related disease was recently named as a novel respiratory 2019 coronavirus disease (COVID-19) by the World Health Organization (WHO) (Xu et al., 2020). Up to date, it is unclear how SARS-CoV-2 interacts with the host antiviral immunity, hence lessons can be learned from previous studies of other members of the coronavirus family and also human pathogenic viruses, such as human immunodeficiency viruses (HIVs) (Fung et al., 2020).

HIVs are the most studied viruses and the best models for understanding the interplay between host antiviral defense and viruses (Fung et al., 2020), contributing to a comprehensive understanding of the viral biology and pathogenesis (Schwetz and Fauci, 2018). The Joint United Nations Program (UNAIDS) data from 2018 reported that more than 77 million people had been diagnosed with HIV, 35 million of whom died as a result of severe disease condition, and currently, approximately 40 million people live with HIV (Schwetz and Fauci, 2018). Besides, HIVs may provide the basic framework for understanding the pathogenicity and cross-species transmission of SARS-CoV-2. In general, many similarities are present between SARS-CoV-2 and HIVs in terms of cross-species transmission (Fung et al., 2020). Based on its genetic diversity, HIVs are classified into two types, namely HIV-1 and HIV-2. The most common and well-studied form is HIV-1 (Pham and Mesplède, 2018). Fung and co-authors made an in-depth comparison between SARS-CoV-2 and HIVs (Fung et al., 2020). According to them, what is learned from HIV is very instructive and highly relevant to SARS-CoV-2 due to the following reasons.

1. SARS-CoV-2 and HIVs are recognized as a potentially zoonotic origin.
2. There are no or mild symptoms when parental viruses of SARS-CoV-2 and HIV infect the reservoir hosts, but severe symptoms are developed when they infect humans. However, this claim is somewhat controversial with the recent study conducted by Liu et al. (2020b) on Malayan pangolins proposed as intermediate hosts of SARS-CoV-2, suffered from serious respiratory disease and failed to be rescued (Liu et al., 2020b).
3. Both SARS-CoV-2 and HIV are derived from their natural reservoirs in animals and spread to humans through cross-species transmission.

Up to date, there is no specific therapeutic drug available against the novel COVID-19. The current steps taken for the management of COVID-19 include isolation of COVID-19 patients, social distancing, provision of supportive medical care, enforcement of travel restrictions, and globally enforced lockdown (Zhang et al., 2020). Many pharmaceutical sectors have already started developing or are in the midst of conducting clinical trials on various potential drugs useful for the treatment of COVID-19 but more insights into the underlying pathobiology are required (Zhang et al., 2020; G.Li and De Clercq, 2020). Thus, this review will comprehensively discuss the taxonomic characteristics of SARS-CoV-2 and HIVs, together with their molecular mechanisms of viral infections and the latest repurpose of existing antiviral drug choices to combat COVID-19.

2. Taxonomy of SARS-CoV-2 and HIV

With the onset of a global pandemic looming over civilization, efforts to correctly classify COVID-19, and definitively study it is ever more pressing. Initially, the outbreak was identified back in December 2019 as a novel coronavirus (2019-nCov) and was later recognized as highly contagious with the impacts of massive global proportions. Pursuant to that, studies have begun to establish the origin and taxonomy of the virus which was then named SARS-CoV-2 by the Coronavirus study group of the International Committee on Taxonomy of Viruses. The disease caused by SARS-CoV-2 was later renamed by WHO to COVID-19 on the 11th of February 2020 (Gorbalenya, 2020). As mentioned, SARS-CoV-2 is a member of the order *Nidovirales*, suborder *Coronavirinae* divided into family *Coronaviridae*, subfamily *Orthocoronavirinae* and further classified into four genera such as *Alpha-, Beta-, Gamma-* and *Delta-coronavirus*. It is the latest addition to an already existing list of 6 other viruses, including 229E, OC43, NL63, HKU1, Middle East respiratory syndrome (MERS) CoV and severe acute respiratory syndrome (SARS) CoV known as human CoVs (HCoVs) due to their ability to cause human infections (Andersen et al., 2020). Aside from NL63 and 229E; which belong to *Alphacoronavirus* and the remaining five viruses come under the *Betacoronavirus* genus. However, SARS-CoV, MERS-CoV, and SARS-CoV-2 are known to cause severe disease leading to death, whereas 229E, OC43, NL63, and HKU1 have only been associated with mild symptoms in infected persons although they are recognized as a potentially zoonotic origins (Andersen et al., 2020; Corman et al., 2018). All members of the *Coronaviridae* contain enveloped, positive-stranded spherical RNA virions with a length of 120–160 nm and are usually decorated with large visible petal-shaped surface projections known as 'spikes' when viewed under an electron microscope (Singh et al., 2020). In addition, members of the *Coronaviridae* share common characteristics, which are outlined in (Table 1). Within the family, there is also another subfamily such as *Torovirinae* comprising two other genera *Torovirus* and *Bafinivirus*. They are different from *Coronaviridae* mainly due to their different tubular virion shape. The morphology of virion, such as *Coronavirinae* has been unraveled, as illustrated in (Fig. 1a). Moreover, the classification of various genera within the subfamily is a little more complicated with high CoV recombination frequency, thus necessitating the development of precise criteria proposed over the years (Corman et al., 2018). Currently, the primary means of establishing their phylogenetic relationship is through the genomic structure, as shown in (Fig. 2). It is based on these differences that a particular host may be infected by specific genus of the virus, for instance, *Alpha-* and *Beta-coronavirus* infects only mammals and *Gamma-* and *Delta-coronavirus* infects primarily birds and some studies suggest the possibility of the latter genera infecting mammals as well (Cui et al., 2019; King et al., 2012; Woo et al., 2012). The specific distinctions between four genera are closely associated with (1) the unique type of nsp1 known as a non-structural RNA-binding protein within their genome which may differ in size and sequence and (2) the presence or absence of a commonly shared accessory gene (Sheikh et al., 2020). Several examples of viruses within the genera with their unique accessory proteins and genome arrangements can be found in (Fig. 3).

The complete SARS-CoV-2 genome sequencing data had begun to emerge as the real gravity of the situation started to loom over the medical personnels who first encountered this novel coronavirus back in December 2019. Their findings have since been published and provided us the information necessary to classify SARS-CoV-2 into its respective group under the *Serbecovirus* (β-B Group) subgenus (Lu et al., 2020b; Chan et al., 2020). The sequence is publicly available on GenBank with the accession number MN908947 possessing 30,474

Table 1
Common Characteristics shared across the members of *Coronaviridae.*

Characteristics	Description	References
Virion	Enveloped and perforated with large petal-shaped 'spiky' surface projections	(Schoeman and Fielding, 2019)
Nucleocapsid	Helical shaped comprising of the genome and multiple copies of a single phosphoprotein (N)	(Grunewald et al., 2018)
Envelope	Made up of 2 membrane protein 1. Integral Protein M – a 200 to 250 aa triple spanning protein 2. Protein S – a N-glycosylated 1100 to 1600 aa class I fusion protein forming 'Spikes'	(Neuman et al., 2011; Song et al., 2004)
Genome	Linear, unimolecular, positive-sense RNA, 26-32 kb long, capped, polyadenylated and structurally polycistronic	(Cui et al., 2019)
Genome organization	Generally, 5'-UTR-replicase-S-M-N-UTR-3'	(Fung et al., 2020; Lu et al., 2020b)
Replicase gene	Overlapped with ORFs 1a and 1b that codes two huge polyproteins, pp1a and pp1ab that are processed autoproteolytically into 16 non-structural proteins involved in genome transcription and replication.	(Sheikh et al., 2020; Singh et al., 2020; Chan et al., 2020; Clavel et al., 1986; Zahoor et al., 2014)
Morphogenesis	Assembly of virion takes place at the smooth intracellular membranes of the endoplasmic reticulum/early Golgi compartments.	(Masters, 2019)

nucleotides with close relations to bat SARS-like coronavirus (CoV) isolate bat SL-CoVZC45 (Genbank accession number MG772933) with 89.1% nucleotide identity similarities (Lu et al., 2020b).

In contrast, the origins of HIV have been a subject of debate since its discovery back in 1980s with many theories floating about and evidences not sufficiently conclusive. What is known is that infected individuals were at risk of developing acquired immune deficiency syndrome (AIDS), which at that time resulted in opportunistic pathogens infecting the individual and due to a pronounced weakened immune system, the individual would succumb eventually to the infection. Current data suggest that over the past three decades, HIV has caused more than 35 million deaths worldwide with 35 million living with the virus (Pharr et al., 2017). HIV is classified with other known immunodeficiency viruses, which belong to phylum Artveviricota, order Ortervirales, and family *Retroviridae*. Further, it has been categorized into subfamily *Orthoretrovirinae* and genus *Lentivirus* including 10 species of viruses, such as feline immunodeficiency virus (FIV), bovine immunodeficiency virus (BIV), simian immunodeficiency virus (SIV) and dog immunodeficiency virus (DIV) (Vemuri et al., 2020). Besides, three other retroviruses, such as Human T-cell Lymphotropic Virus type 1, 2, 3 (HTLV 1, 2, 3) exist within the same subfamily but genus *deltaretrovirus* also affects the immune system in humans (Calattini et al., 2005).

As mentioned earlier, HIV has been categorized into two types; HIV-1 and HIV-2, the former being known as a more pathogenic than the latter, making up the majority of AIDS cases around the globe, whereas HIV-2 mainly infects individuals in West Africa (Cloyd et al., 2000). In general, the most plausible route of evolution can be established by genomic sequence of HIV, while its origin is yet to be understood. In 1986, the genomic analysis found that HIV-2 virus was morphologically similar but genetically different from type 1 and caused more serious AIDS disease in western Africa (Jaffar et al., 2004). Another genomic study showed that HIV-2 is firmly associated with the simian immunodeficiency virus (SIV) isolated from macaque monkeys (Nakayama and Shioda, 2015). Since then, the simian close relatives have been further expanded with more and more species of primates in Sub-Saharan Africa found to house similar viruses collectively named SIV with special suffixes denoting their species of origin. In general, SIV-derived host species have been found to be non-pathogenic, but can become pathogenic once they cross the species (Meyerson et al., 2018); resulting in the discovery of current pandemic HIV1 strain (group M or main) that is similar to SIV_{cpz} in Chimpanzees (*Pan troglodytes*) after closer investigation. In addition, the natural host of viruses was identified in Cameroon (Hahn et al., 2000; Keele et al., 2006).

The morphological structure of HIV is usually spherical, enveloped with 80–100 nm in diameter, and 8 nm surface glycoprotein projections. The internal structure of the virus nucleocapsid, such as a rod or truncated cone-shaped has been shown in (Fig. 1b). The viral genome consists of a linear dimer of positive-sense ssRNA with each monomer at approximately 7–13 kb in size. Each monomer is polyadenylated at the 3′ end and contains a cap structure at the 5′ end. Within the virus, proteins make up about 60% of the biomolecular content, including two envelope proteins, SU (surface) and TM (Transmembrane), 3–6 internal and non-glycosylated structural proteins comprising of CA (capsid), NC (nucleocapsid), MA (matrix) and some unspecified functional proteins. Meanwhile, other proteins such as PR (protease), IN (integrase), and RT (reverse transcriptase) also exist inside the virus.

HIV viral genome follows the common pattern within the subfamily

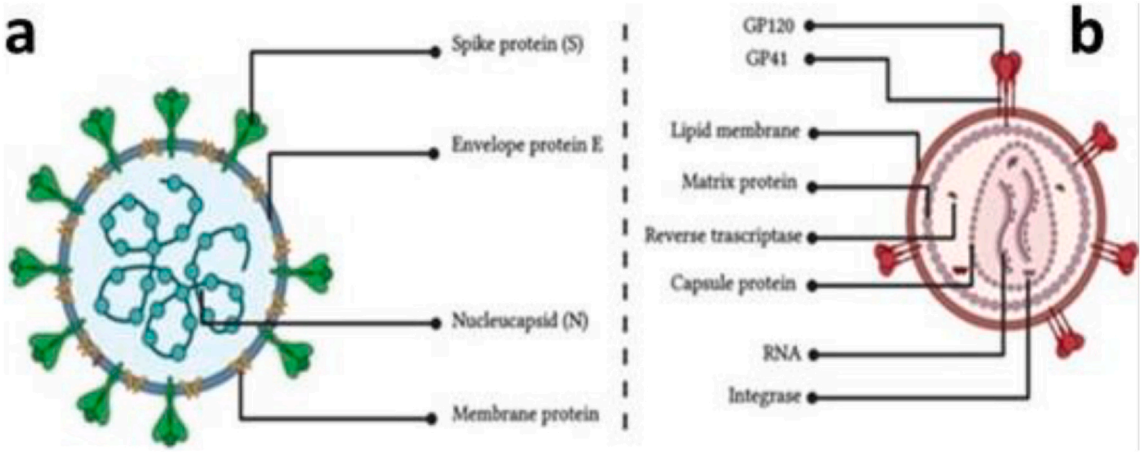

Fig. 1. Schematic illustration of the virion morphology of coronavirus (a) and HIV (b).

Fig. 2. The general genome structure of *Coronaviridae* shared across the family, consisting of a positive-sense ssRNA genome of 27–32 kb in size. Starting from the 5′-terminal with approximately two-thirds of the genome encoding for polyprotein, pp1ab, which is cleaved into 16 non-structural proteins that are involved in genome transcription and replication. The 3′-terminal end possesses the primary structural genes encoding for 'spike' (S) protein, envelope (E) protein, membrane (M) protein and nucleocapsid (N) protein.

Orthoretrovirinae, which carries two copies with the arrangement order: 5′-*gag-pro-pol-env*-3′, each at approximately 9.3 kb in size. A schematic illustration of the HIV genome is shown in (Fig. 4) with comparisons made with other species within the *Lentivirus* genus. Upon successful infection and incorporation of retroviral DNA into the chromosomal DNA of the host, cellular RNA polymerase II transcribes DNA into virion RNA and mRNA which serves as a template for the translation of *gag*, *pro* and *pol* genes into the resulting protein from the 5′-half end. As a result, polyprotein precursors are formed and cleaved to produce the structural proteins such as PR, IN, and RT. The other half of mRNA 3′ end is translated into viral envelope precursors with other accessory proteins. In general, the unique sequences of viruses give each genus of a specific viral family its distinguishing characteristics allow its classification into the respective genus, which is *Lentivirus* in case of HIV. In addition to the primary structural genes reported, members of the *Lentivirus* genus also have additional genes, for instance, accessory protein genes *vif*, *vpr*, *vpu, nef*, and regulatory protein genes *tat* and *rev*. Several additional activities have been ascribed to the resulting proteins transcribed by these genes (secondary activities) which suggest the multifunctional role they play but generally their primary activities are highly conserved (Faust et al., 2017). A summary of these accessory proteins and their role has been shown in (Table 2).

3. The emergence and transmission

SARS-CoV-2 was first reported in December 2019 and reportedly originated from the Huanan sea wet market in Wuhan city (Andersen et al., 2020; Zhu et al., 2020b; Singhal, 2020). Its unprecedented spread leads to a thorough investigation by Chinese researchers, who noticed that the cluster of atypical pneumonia cases emerged from the zoonotic transmission and showed > 95% homology with bat coronaviruses and > 70% similarity with the previous SARS-CoV (Lu et al., 2020b; McIntosh, 2020). Thus, Chinese Health Authorities identified the outbreak as a novel coronavirus (COVID-19) (Lu et al., 2020a). Although environmental samples taken from the market tested positive, researchers considered the possibility of human-to-human transmission in other geographical areas after people returned from Wuhan celebrating the Chinese New Year (CNY) with their families (Wang et al., 2020; Chen et al., 2020). In this context, one study showed a significant correlation between domestic train transportation and the number of cases imported to other provinces in China. Besides, non-stop passenger flights were also linked to the number of cases reported abroad, subsequently the cause of this pandemic (Rodríguez-Morales et al., 2020). Evidence suggests that virus is transmitted by respiratory droplets, direct contact, and airborne transmission. While analysis of confirmed and suspected cases of COVID-19 suggested that novel virus could go beyond the respiratory tract (Peng et al., 2020). More interestingly, the study also found that virus can enter the body through eye exposure (J.P.O. Li et al., 2020a).

Notably, several asymptomatic cases have emerged across the globe, arguably the cause of such widespread transmission (Bai et al., 2020). Earlier this year, Italy declared a state of emergency after registering two cases from Wuhan tourists with suspected symptoms of coronavirus after they arrived in Rome (Giovanetti et al., 2020). Similarly, the USA confirmed the first positive case of SARS-CoV-2 identified in a woman in her 60's, who had returned from China with good health in mid-January. Later, her husband was also tested positive and admitted to the hospital. Although he did not travel but was considered to be in close contact with his wife (Ghinai et al., 2020). Similarly, a 50-year-old female entered the UK from Hubei province without previous medical history and no regular medications. After arrival, she developed symptoms of malaise and fever, accompanied by a sore throat and dry cough within three days (Lillie et al., 2020).

As some cases show delayed symptoms, the possibility of human-to-human transmission could occur during the asymptomatic incubation period (X.Li et al., 2020c; Backer et al., 2020). Until an appropriate diagnostic cure is found, researchers have alerted countries to maintain a distance of one meter from infected persons to reduce the risk of transmission (Mehraeen et al., 2020). Subsequently, many countries have now introduced movement control orders and lockdowns as preventative measures to curb the spread of the virus (Hamzelou, 1981), urging their citizens to maintain social distance to minimize the spread of the virus.

In recent history, another deadly virus called the human immunodeficiency virus (HIV) had emerged, which is the retrovirus responsible for the acquired immunodeficiency syndrome (AIDS). As a common disease in Asia, the concurrence of these diseases could present an alarming problem globally. Recently, Zhu and colleagues noted that "HIV infected patients need to be regarded as a vulnerable group," after co-infection of COVID-19 and HIV was reported in a patient in Wuhan, China (Zhu et al., 2020a). Previously, HIV-1 emerged in young homosexual men in 1981 (Brodie et al., 2004). Five years later, HIV-2 virus was discovered with similar morphology to HIV-1, but antigenically distinct, which increased AIDS cases reported in patients from western Africa in 1986 (Clavel et al., 1986). Nonetheless, HIV-2 viral strain was distantly related to HIV-1 and both strains were acquired by humans from non-human primates infected with simian immunodeficiency virus (SIV) (Heeney et al., 2006).

Scientists believed that SIV was transmitted to humans after contact with the blood of infected chimpanzees during bushmeat handling. Notably, the virus mutated into HIV from its origins and gradually spread from Africa to other parts of the world (Sharp and Hahn, 2011; Ayouba et al., 2013; Sousa et al., 2017). Thus, confirming the occurrence of both viruses (HIV-1 and HIV-2) as a result of zoonotic transmission from infected primates. In general, human-to-human spread is known to be transmitted from mother to child, and during unprotected sexual intercourse between couples (Kassa, 2018). When HIV infected body fluids, including blood, breast milk, semen, vaginal, and rectal secretion come into contact with mucous membrane in the mouth, rectum, penis, and vagina, it destroys the tissue or injects directly into the bloodstream by a needle or syringe (Hladik and McElrath, 2008; Shaw and Hunter, 2012).

In summary, it is still unknown whether any identified interrelationship presents between HIVs and SARS-CoV-2. Despite the remarkable number of patients infected with HIV and novel COVID-19 separately, which extends to cover a wide zone in Asia and worldwide. There are very few reports on the SARS-CoV-2 infection among patients infected with HIV (Joob and Wiwanitkit, 2020).

4. Mechanism of infection

It has been observed that HIV targets the specific CD4+ immune cells, including T cells, macrophages, and dendritic cells, resulting in a significant reduction in the number of these immune cells in HIV-infected patients (Lane, 2010). These CD4+ T cells (known as helper cells) are the backbone of the immune system where they activate B

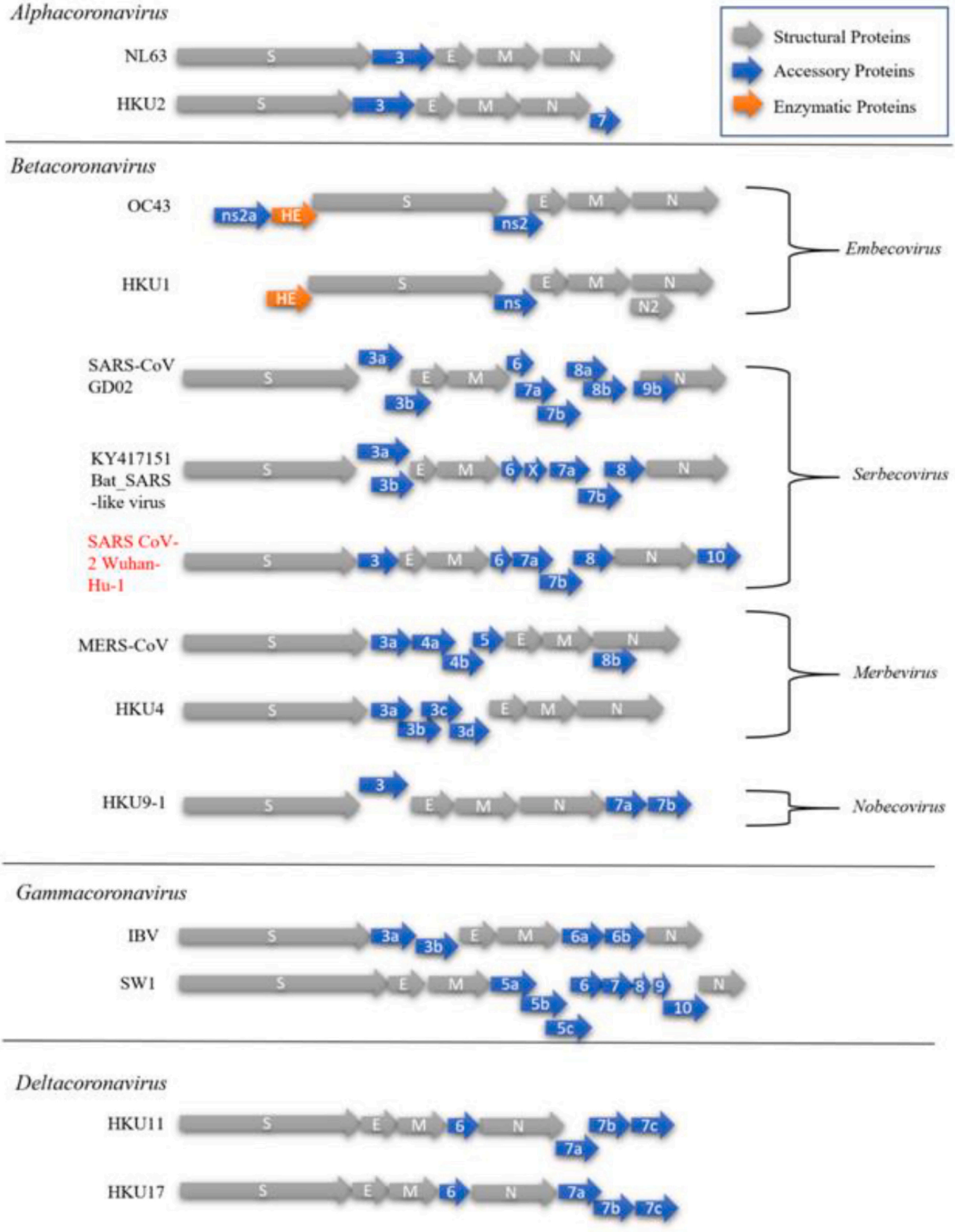

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Fig. 3. Comparison of various coronavirus members of their respective genera: NL63 associated with lower respiratory tract disease, *Rhinolophus* bat coronavirus HKU2, Human coronavirus OC43, HKU1 possessing the enzyme haemagglutinin-esterase, severe acute respiratory syndrome coronavirus (SARS-CoV) strain GD02, Bat (SARS)-like Virus KY417151, severe acute respiratory syndrome coronavirus (SARS-CoV-2) isolated from Wuhan in December 2019 Genbank Accession number: MN908947 (Wu et al. 2020), Middle East respiratory syndrome coronavirus (MERS-CoV), Bat coronavirus HKU 14–1, Bat coronavirus HKU9-1, Infectious bronchitis virus (IBV), Beluga whale coronavirus SW1, Bulbul coronavirus HKU11 and Sparrow coronavirus HKU17.

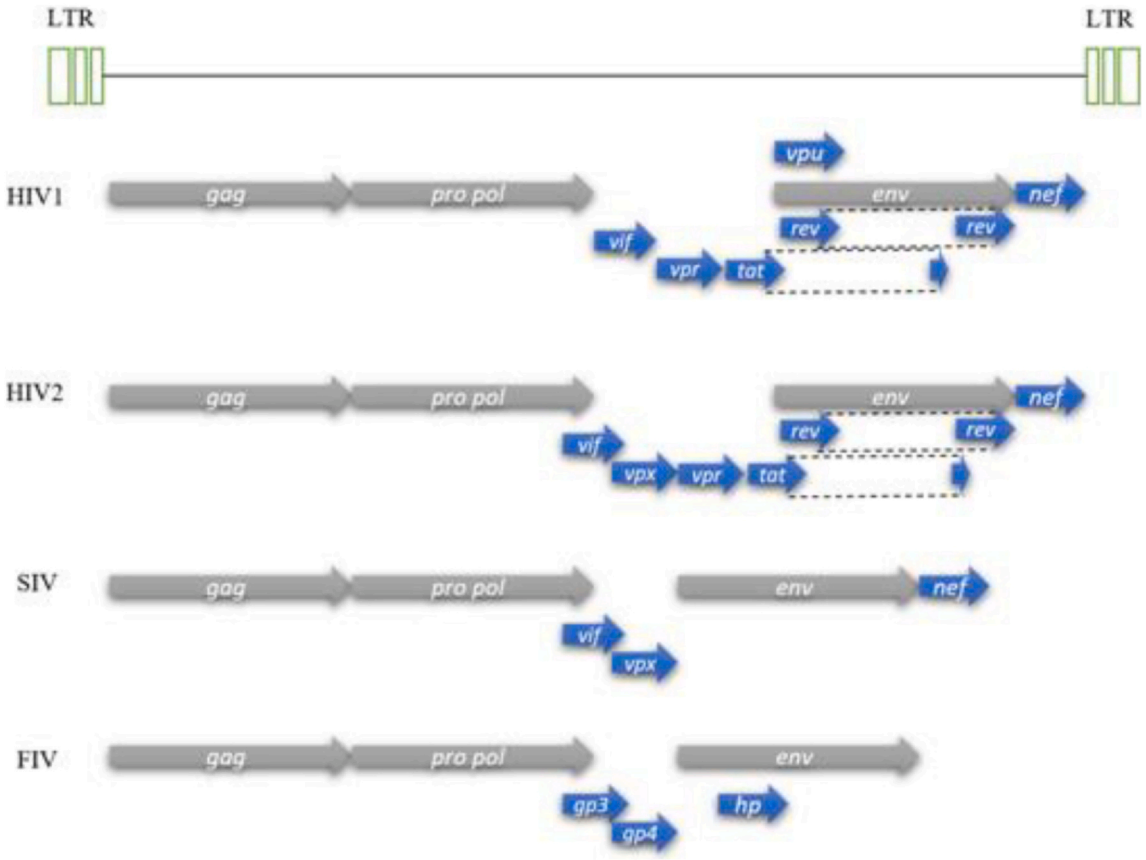

Fig. 4. Comparison between various members of the *Lentivirus* genus reference genome. Human Immunodeficiency Virus 1 (HIV1), Human Immunodeficiency Virus 2 (HIV2), Simian Immunodeficiency Virus (SIV) and Feline Immunodeficiency Virus (FIV).

Table 2
List of accessory genes within the HIV genome and their associated functions.

Gene	Primary function	Secondary Function	References
vif	• Counteract antiviral effects of host APOBEC3 (A3) innate immune proteins.	• Forms dimer with CBFβ to alter gene expression in infected T cells, primarily on RUNX1 binding sites. • Remodels cellular phosphor-proteome resulting in more than 200 cellular proteins hyperphosphorylated.	(LaRue et al., 2010; Greenwood et al., 2016; Kim et al., 2013)
vpr	• Transactivation of LTR • Nuclear import of the preintegration complex • Cell cycle arrest and apoptosis. • Activation of the DNA damage response.	• Increase transcription from HIV-1 LTR. • Induces other cellular genes mainly in the interferon-stimulated genes	(Lai et al., 2005; Roshal et al., 2003; Ziebuhr, 2005; Zimmerman et al., 2006)
vpu	• Promotes viral release from host • Remove membrane-bound protein that inhibits viral replication via ubiquitination.	• Deregulation of NF-kB pathway via downregulation of BST-2/Tethrerin.	(Galão et al., 2012; Roy et al., 2014)
nef	• Modulate signaling by tyrosine kinases. • Modulate host trafficking through binding with clathrin adaptor complexes	• Activates NF-kB initiate positive transcription feedback loop for Tat.	(Geyer et al., 2001; Sauter et al., 2015)
tat	• An HIV transcription factor that supports the generation of full-length viral mRNAs.	• Induces transcription and secretion of chemokines which attracts T cells and monocytes increasing infectivity.	(Feinberg et al., 1991; Izmailova et al., 2003)
rev	• Directs exports of viral messages that are translated into viral proteins, providing genomic RNA for packaging and budding virion	• Indirect regulation of HIV-1 transcription.	(DiMattia et al., 2010; Felber et al., 1990)

cells, macrophage, and cytotoxic T cells to secrete antibodies, destroy ingested microbes and kill the infected cells, respectively (Laidlaw, 2016). The HIV membrane contains a transmembrane glycoprotein called glycoprotein-41 (GP41) and surface glycoprotein, namely glycoprotein-120 (GP120), which binds to CD4 receptors on the surface of CD4+ cells (Pancera et al., 2014). There are two other chemokine co-receptors known as C−C chemokine receptor 5 (CCR5) and C−C chemokine receptor 4 (CXCR4), which facilitate HIV binding and infusion into CD4+ cells (Didigu et al., 2014). CXCR4 co-receptor is expressed in many peripheral T-cells lymphoma found in the lymphatic sides, including lymph nodes, bone marrow, and spleen (Machado et al., 2009). However, CCR5 is highly expressed on the surface of T cells, macrophages, dendritic cells, eosinophils, and microglia (Moore et al., 2004). The binding of GP120 to CD4 receptor leads to a change in the envelope structure of virus, which allows the co-receptor, either CCR5 or CXCR4 (CXCR4 for T-tropic HIV strains, and CCR5 for M-tropic HIV strains) bind to a specific domain in the gp120. After binding, the N-terminal fusion peptide (GP41) penetrates in the host cell membrane, followed by entry of viral capsid into the cytosol of T cell. After penetration, virus removes and exposes its capsid, which contains the RNA genome and its associated enzymes (reverse transcriptase and integrase) into the host cell (Naif, 2013). The virus produces complementary DNA (cDNA) by transcribing its single-standard RNA based on reverse transcriptase activity for producing duplicate strands of viral DNA. However, complete viral DNA migrates to the nucleus and integrates with DNA inside the host cell and unfortunately affects the cellular activity. The integrated DNA is used to generate mRNA, thus synthesizing the viral proteins and allowing the new virus copy to develop. It has been observed that virus sabotages the CD4+ immune T cells for replication, which leads to increase virus load in the blood and a significant decrease in CD4+ T cells (Goodsell, 2015). Interestingly, some researchers found another mechanism of HIV destruction of CD4+ T cells (Bolton et al., 2002; Yue et al., 2005). They observed that depletion of CD4+ T cells by apoptosis pathway because of direct HIV infection was only 5–10% of the total CD4+ T cell pool. It has been found that HIV enzyme (integrase) plays a crucial role in the activation of DNA-PK sensor of host cell, which activates the apoptotic cascade inside the cell. However, another HIV enzyme (protease) activates the caspase-8 that further triggers the apoptosis of infected cells. Besides, specific HIV proteins display on the surface of infected CD4+ T cells, which alarm CD8+ T cells to destroy the infected CD4+ T cells. The immune system reacts by producing antibodies, such as anti-HIV antibodies, which stick to the infected CD4+ T cells and mark their destruction by other immune cells (Selliah and Finkel, 2001). However, it has been observed that indirect effect of HIV infection results in majority of CD4+ T cells death, which causes immune deficiency. The direct effect of HIV to CD4+ T cells triggers the expression of interferon-gamma induced protein-16 (IFI-16), followed by the activation of inflammatory cascade inside the infected cell, which ends up with cellular self-destruction called pyroptosis (Doitsh et al., 2014; Monroe et al., 2014). The caspase-1 activated by high expression of IFI-16 triggers the production of cytokines, especially interleukin-1 beta (IL-1β) inside the infected cells (Lupfer et al., 2015). The high production of IL1-β leads to the creation of inflammatory environment inside the cell, resulting in the initiation of apoptosis (Feria et al., 2018). The infected cells lead to release of interleukin-1 beta (IL-1β) to the outside cellular environment, which contributes to the activation of pyroptosis in the non-affected cells, causing a considerable loss of CD4+ T cells (Doitsh et al., 2014).

Unlike HIV, the exact mechanism how COVID-19 induces immune defect is still unknown; however, it could be similar to the previous coronaviruses, including the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). These viruses induce low level of lymphocytes abnormality in blood, or it is known as lymphopenia related to HIV infection. The binding of coronavirus to the host cell required a specific class I viral glycol- transmembrane-protein, such as S protein on the surface of the virus envelope. It needs a specific receptor on the host cells called angiotensin-converting enzyme 2 (ACE2) receptor (Andersen et al., 2020; Dhama et al., 2020). ACE2 is an enzyme spread in many cell membranes of different organs, including lungs, arteries, heart, kidney, and intestines; it plays a significant role in blood pressure regulation. The dramatic reduction in the peripheral CD4+ and CD8+ T cells is one of the symptoms in COVID-19 cases related to HIV infection (Liu et al., 2020a; Diao et al., 2020). Besides, over circulation of proinflammatory cytokines and chemokines, including interleukins (IL-1β, IL1RA, IL2, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL12p70, IL13, IL15, IL17A), eotaxin, basic fibroblast growth factor (FGF2), granulocyte-colony stimulating factor (GCSF), granulocyte-macrophage colony-stimulating factor (GMCSF), Interferon-gamma (IFNγ), IFN-γ-inducible protein-10 (IP10), chemokines (Monocyte chemoattractant protein-1 (MCP1)), macrophage inflammatory proteins-1A (MIP1A), macrophage inflammatory proteins-1B (MIP1B), platelet-derived growth factor subunit B (PDGFB), C−C motif chemokine ligand 5 (CCL5)), and tumor necrosis factor (TNFα) was observed in the acute stage of positive COVID-19 patients (Rothan and Byrareddy, 2020; Huang et al., 2020). Moreover, it has been observed that level of NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome was high in patients infected with COVID-19, which triggers the release of IL-1β and IL-18 (Freeman and Swartz, 2020; Tang et al., 2020; Chen et al., 2019). However, a hyper-immune response was also reported during the clinical course of SARS-CoV infection that is responsible for the high morbidity of SARS-CoV. The high production of C−C motif chemokine ligand 2 (CCL2), C-X-C Motif Chemokine Ligand 9 (CXCL9), C-X-C Motif Chemokine Ligand 10 (CXCL10), interleukins (IL-1, IL-6, IL-8) with interferon-gamma (IFN-γ), and transforming growth factor-beta (TGF-β) occurred in the acute stage of SARS-CoV infection triggering the cytokine storm (Cameron et al., 2008; Huang et al., 2005). In addition, T cell lymphopenia has been reported in several SARS-COVID patients, where the total number of CD4+ and CD8+ T cells drastically decreased within two weeks of infection (Cui et al., 2003). The investigation by Jiang et al. (2019) proves the activation of pyroptosis during MERS-CoV infection. Like HIV infection, MERS-CoV activates caspase-1 in the spleen with high circulating amount of TNF-α, IL-1β, IFN-γ and IL-6, and upward stimulation of macrophages (Jiang et al., 2019). Taken together, the pro-inflammatory molecules released from the immune cells during the onset of COVID-19 infection create an acute inflammatory environment similar to that recorded in HIV exposure, which consecutively activates the pyroptotic cascade of immune cells. Notably, the immune deficiency is more severe in case of coronaviruses because it occurs at the early stage of infection (within a few days), while it takes a longer time for HIV after ten years. Fig. 5 explains the molecular mechanism and cell death of COVID-19 and HIV.

5. Latest therapeutic potential of antiviral agents against COVID-19

At present, there is no effective antiviral therapy available for treating the latest respiratory 2019 coronavirus infection. Therefore, the development of an active antiviral agent and vaccine is crucial to stop the COVID-19 pandemic. The economic and social challenges produced by this outbreak also demand urgent interventions worldwide. An earlier study on MERS- and SARS-CoV has allowed expediting the discovery of viable drugs to combat the new outbreak of SARS-CoV-2. However, there is no therapeutic drug that targets MERS- and SARS-CoV which has progressed beyond phase-1 studies at present.

Chloroquine is a primary therapeutic drug used to prevent and treat patients infected with malaria. Fig. 6a shows the chemical structure of chloroquine. Recently, the National Center for Biotechnology Development (NCBD) in China stated that chloroquine is an effective drug that could be used to treat patients infected with novel COVID-19. Notably, the chloroquine therapeutic drug repurposing has been

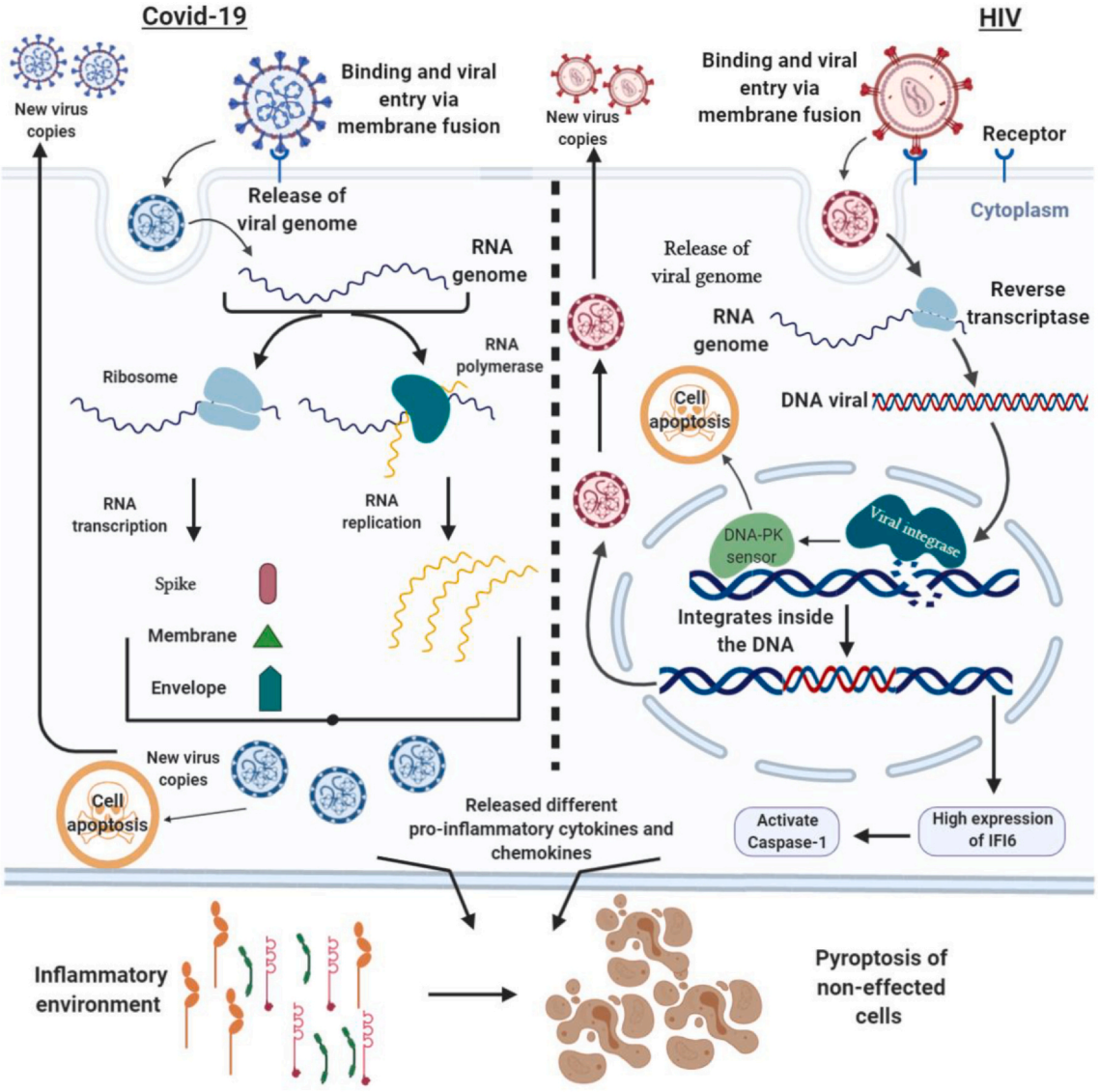

Fig. 5. Crosstalk of the infection mechanism and cell death of COVID-19 and HIV.

studied in hospitals in Beijing, Guangdong Province in South China, and Hunan Province in central China. The earlier studies by Gao et al. (2020) conducted in China proposed that approximately a hundred patients infected with SARS-CoV-2 were treated with drug chloroquine; as a result, a rapid fall in fever and improved computed tomography (CT) scan images of the lung were observed, and patients also needed a short recovery time compared to the control group, without any side effects. Therefore, the Chinese Medical Board (CMB) has suggested to include chloroquine as a therapeutic drug in the guidelines for treating the SARS-CoV-2. Probably, chloroquine is the first therapeutic drug to be used for the patients infected with SARS-CoV in China and worldwide. However, the more extended use of chloroquine could produce severe side effects, such as cardiomyopathy (Bernstein, 1991; Ratliff et al., 1987) and the presence of some reports on macular retinopathy as a minor risk caused by this drug (Cubero et al., 1993). A survey of the patients infected with SARS-CoV-2 for adverse side effects of chloroquine treatment is yet to be conducted. Chloroquine was considered the best therapeutic drug choice available for treating SARS-CoV-2 infected patients in hospitals. Recently, the WHO has advocated a solidarity clinical trial for COVID-19 treatments. The solidarity clinical trial will compare four treatment choices, including chloroquine/hydroxychloroquine, remdesivir, lopinavir/ritonavir, and lopinavir/ritonavir plus interferon beta-1a against standard therapy and determine their relative efficacy against COVID-19 (World Health Organization, 2020).

Remdesivir (GS-5734) is the chief antiviral therapeutic drug that could be used for combating SARS-CoV-2. Remdesivir is a class of adenosine nucleotide analogue drug with a wide range of antiviral activity towards pneumo-viruses, paramyxoviruses, filoviruses, and pathogenic strains of coronaviruses, such as MERS- and SARS-CoV (Sheahan et al., 2017). Fig. 6b shows the chemical structure of remdesivir. The pharmacokinetic trials have been accomplished, and clinical studies are being conducted for testing the effectiveness of remdesivir in the treatment of Ebola virus (Mulangu et al., 2019). In general, earlier studies have found that adenosine nucleotide analogues are less effective against coronaviruses because of the proofreading exonuclease of the virus. However, the drug remdesivir was effective against MERS- and SARS-CoV, and also many strains of bat-CoV (Sheahan et al., 2017). A study reported that remdesivir showed an effective half-maximum concentration (EC50s) of 0.074 μM for MERS-CoV and 0.069 μM for SARS-CoV (Brown et al., 2019). Notably, in-vitro studies have found that therapeutic drug remdesivir is also useful in the EC50 submicromolar scale against a wide range of significantly divergent coronaviruses, such as human endemic CoVs, 229E (HCoV-229E) and OC43 (HCoV-OC43). Hence, the remdesivir has a broad-

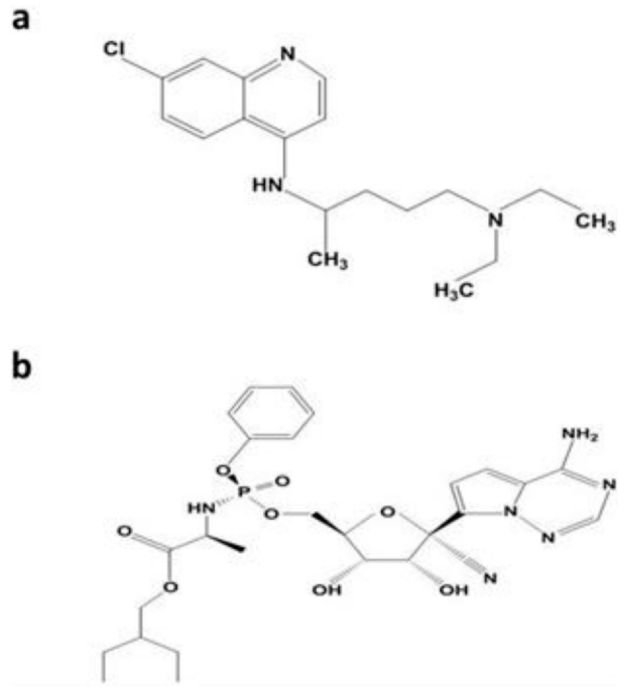

Fig. 6. Chemical structure of (a) chloroquine and (b) remdesivir.

spectrum activity against CoVs (Brown et al., 2019). The prophylactic administration of remdesivir significantly decreased the viral titers < 2 on the lung in SARS-CoV mouse model. In addition, remdesivir improved respiratory function and the clinical symptoms of illness compared to control animals (Sheahan et al., 2017). The authors reported that comparable findings with MERS-CoV were attained in prophylactic studies conducted with MERS-CoV transgenic mouse model (Cockrell et al., 2016). They found that the enzyme carboxylesterase 1c (Ces1c) was deleted and receptor (dipeptidyl peptidase 4, hDPP4) of humanized MERS-CoV was expressed in order to increase the pharmacokinetics of nucleotide prodrugs. Another study conducted by Agostini et al. (2018) reported that two mutations were recognized, such as V553L and F276L in the RNA-dependent RNA polymerase gene of the virus after 23 passages of remdesivir drug (Agostini et al., 2018). They also observed that these changes in amino acid reduced the burden of virus and lessened the pathogenesis of SARS-CoV in mice. In recent months, the prophylactic efficacy of remdesivir was also tested in a rhesus macaque (non-human primate) MERS-CoV infection model (de Wit et al., 2020). When the treatment with prophylactic remdesivir was started 24 h before inoculation, MERS-CoV was found to be inhibited from replicating in the respiratory tissues and prevented from causing clinical disease, which inhibited the development of lung lesions. The same findings were obtained when treatment with remdesivir drug was initiated 12 h after the virus inoculation (de Wit et al., 2020). The remdesivir therapeutic drug safety data are readily available for humans (Mulangu et al., 2019); hence, human studies can be conducted to assess the effectiveness of this compound towards novel coronaviruses.

The Food and Drug Administration (FDA) approved the therapeutics against MERS- and SARS-CoV that have been assessed for antiviral activity. For instance, lopinavir (LPV), a protease inhibitor of HIV-1, was tested to combine with ritonavir (RTV) in order to enhance the half-life of LPV. The combination of these two drugs (LPV/RTV) was found to be more effective in patients against SARS-CoV and in-vitro study. The calculated EC50 was 4 μg/ml for the fetal rhesus kidney-4 cells (Chu et al., 2004). Meanwhile, Chan and coworkers reported that LPV/RTV also declined clinical sores, weight loss, and progression of disease in marmosets infected with MERS-CoV (Chan et al., 2015). However, the antiviral activity of LPV towards MERS-CoV in the in-vitro study remains controversial. Another study conducted by Chan et al. (2013) found no optimal EC50 in the Vero cells, whereas EC50 was reported to be 8 μM in the Huh7 cells in a different study (de Wilde et al., 2014).

It was found that infections with MERS-CoV were mediated by replication of the virus and host inflammatory responses after clinical observations in both humans and animals. Those studies had suggested the use of combination therapies including interferons I and II. However, interferon-beta (IFNb) reduced the replication of MERS-CoV in the tissue culture and showed the best efficacy with 1.37–17 IU/ml EC50s (Chan et al., 2013; Hart et al., 2014). From the study on marmosets infected with MERS-CoV, Chan et al. (2015) reported the clinical improvement with the use of LPV/RTV with IFNb. Also, the clinical randomized control trials were started in Saudi Arabia in order to determine the efficacy of combinations of therapies, such as IFNb and LPV/RTV in improving the clinical outcomes against MERS-CoV (Arabi et al., 2018). Notably, China has launched another controlled trial to test the effectiveness of IFNα-2b and LPV/RTV in hospitalized SARS-CoV-2 patients (ChiCTR2000029308).

In addition, the therapeutic and prophylactic activities of LPV/RTV-IFNb and remdesivir were compared in a transgenic mouse model infected with MERS-CoV (Sheahan et al., 2020). It was found that remdesivir reduced lung viral titers, virus replication, and improved the pulmonary function. At the same time, prophylactic combined therapeutics, such as LPV/RTV-IFNb, only resulted in a moderate decline in viral titers and did not produce any effects on other parameters of disease. The combined therapy boosted pulmonary function but did not influence viral replication (Sheahan et al., 2020). Thus, it was observed that remdesivir has shown to be effective for treating MERS-CoV infections compared to LPV/RTV-IFNb.

Another antiviral prodrug, Ribavirin is a guanosine analogue used to treat many infections caused by viruses, such as hepatitis C respiratory syncytial virus, and patients coinfected with HIV and hepatitis B. In 1980, it was launched to the marketplace for treating the respiratory syncytial virus, especially in children. In most cases, it is used in combination with interferon (IFN). Falzarano and co-authors found promising results when ribavirin was combined with IFNα-2b against the rhesus macaque model infected with MERS-CoV (Falzarano et al., 2013), but there have been some contradictory data on the MERS-CoV infected patients treated with IFNα2a or IFNβ1 and ribavirin (Arabi et al., 2017). Besides, ribavirin also produces adverse side effect such as decreasing haemoglobin concentrations in patient with respiratory disorder that could not be appropriate for use against SAR-CoV-2. In addition, various other antiviral therapeutic drugs/cocktails, including favipiravir, nitazoxanide, ganciclovir, acyclovir/penciclovir, and the latest FDA-approved ivermectin are listed in Table 3.

In summary, the repurposing of preexisting antiviral therapeutic drugs is finite, so it is almost inevitable that both new and repurposed drugs will be required to treat COVID-19. Therapeutic drug choices in response to COVID-19 are urgently required and fortunately, some of the preexisting antiviral therapeutics are already progressing into human clinical trials.

6. Impact of SARS-CoV-2 on HIV therapy

SARS-CoV-2 has dramatically altered the daily lives of people worldwide. This virus has already enforced social distancing, travel restrictions, and provision of supportive medical care, resulting in significant disruptions to routine functioning. With regard to the social nature of individuals, people are trying to adjust their lives with SARS-CoV-2 for the foreseeable future. Moreover, it is also crucial for the healthcare professionals (e.g., physicians, psychologists, etc.) to comprehend about the provision of healthcare therapy across time and how the biological impacts of SARS-CoV-2 can affect people with HIV (PWH). Besides, people with HIV (PWH) are placed at a higher risk for contracting and developing complications related to COVID-19. Given

Table 3
Listed repurposed antiviral drugs in clinical development against COVID-19.

Drug/cocktail	Mode of action	Status and anti-infective mechanisms	Target diseases	References
Chloroquine	9-aminoquinolin	Status: approved, vet-approved, investigational; Mechanisms: the drug increasing endosomal pH, inhibitors of autophagy, and immunomodulating	Malaria, and autoimmune disease	(Savarino et al., 2003; Golden et al., 2015)
Remdesivir (GS-5734)	The prodrug of Nucleotide analogue	Status: experimental; Mechanisms: the drug interfering with the post-entry of virus	MERS, SARS, and Ebola	(Agostini et al., 2018; Tchesnokov et al., 2019; Lo et al., 2019)
Lopinavir/ Ritonavir	Protease inhibitors	Status: approved; Mechanisms: inhibiting the protease of HIV-1 for protein cleavage; as a result, immature or non-infectious viral particles	HIV/AIDS, MERS, and SARS	(Chu et al., 2004; Oldfield et al., 2005; Arabi et al., 2020)
Lopinavir/ritonavir, ASC09/ritonavir, with and without umifenovir	Protease inhibitors	Status: experimental, approved; Mechanisms: lopinavir/ritonavir are protease inhibitors; ASC09 is a protease inhibitor of HIV-1; Umifenovir is an entry inhibitor for influenza	HIV/AIDs, and influenza	(Harrison, 2020)
Ribavirin	Synthetic guanosine Nucleoside	Status: approved; Mechanisms: the drug interfering with the viral mRNA synthesis, also a broad-spectrum antiviral activity for both RNA and DNA	HCV, MERS, and SARS	(Chung et al., 2018; Arabi et al., 2019)
Different combinations of lopinavir/ritonavir and baloxavirmarboxil/favipiravir	Favipiravir is a guanine analog RNA-dependent RNA polymerase inhibitor, and baloxavirmarboxil is a Cap-dependent endonuclease inhibitor	Status: approved; Mechanisms: favipiravir is a guanine analog RNA-dependent RNA polymerase inhibitor, and baloxavirmarboxil is a Cap-dependent endonuclease inhibitor approved for influenza A and B	Influenza A, and B	(Harrison, 2020)
Oseltamivir	Neuraminidase inhibitor	Status: approved; Mechanisms: the drug inhibiting the viral neuraminidase activity, and also inhibiting the infectivity and viral replication	Influenza (A) viruses	(McQuade and Blair, 2015; Jefferson et al., 2014)
Oseltamivir, ritonavir/oseltamivir, ASC09/ oseltamivir	Oseltamivir is a sialidase inhibitor	Status: approved; Mechanisms: oseltamivir is a sialidase inhibitor approved for influenza	Influenza	(Harrison, 2020)
Interferon α-2b alone or together with ribavirin and lopinavir/ritonavir	Interferon α-2b is a recombinant cytokine and ribavirin is a guanine derivative	Status: experimental, approved; Mechanisms: interferon α-2b is a recombinant cytokine protein with antiviral activity and ribavirin is a guanine derivative approved for viral infections	Cancer, hepatitis B, and C	(Harrison, 2020)
Ganciclovir	Nucleoside analog	Status: investigational, approved; Mechanisms: a potent inhibitor of family Herpesvirus, such as cytomegalovirus	HIV/AIDS-related cytomegalovirus infections	(Al-Badr and Ajarim, 2018)
Acyclovir/Penciclovir	Nucleoside analog	Status: approved; Mechanisms: it is a synthetic derivative of acyclic guanine, as a result of chain termination	VZV, HSV	(Chung et al., 2018)
Favipiravir (T-705)	Nucleoside analog: polymerase inhibitor of viral RNA	Status: investigational; Mechanisms: inhibiting viral reproduction by acting on its genetic copying without influencing on host cellular nucleic acid	Influenza A(H1N1), Ebola	(Shiraki, 2018; Cardile et al., 2017)
Nafamostat	Synthetic inhibitor of serine protease	Status: investigational; Mechanisms: inhibiting the membrane fusion through preventing the release of cathepsin B; role as an anticoagulant activity	MERS, Ebola, MERS, and influenza	(Hsieh and Hsu, 2007; Nishimura and Yamaya, 2015)
Azvudine	Inhibitor of reverse transcriptase	Status: experimental; Mechanisms: inhibitor of reverse transcriptase against AIDS/HIV-1	HIV-1/AIDS	(Harrison, 2020)
Nitazoxanide	Antiprotozoal agent	Status: approved, vet-approved, investigational; Mechanisms: modulating the growth, survival, and proliferation of intracellular and extracellular viruses, protozoa, bacteria (microaerophilic and anaerobic), and helminths	Human/animal coronaviruses	(Rossignol, 2014; Rossignol, 2016)
Ivermectin	Antiparasitic agent	Status: FDA-approved, vet-approved, investigational; Mechanisms: targeting the glycine receptor subunit α-3 and gamma-aminobutyric acid receptor subunit β-3 in human	Onchocerciasis, strongyloidiasis, and scabies	(Caly et al., 2020)

the long-term HIV prognosis, it is important for PWH to regularly attend their healthcare providers and adhere to therapy (National Institute of Allergy and Infectious Disease, 2020). The treatment of PWH can be affected due to stay at home orders enforced by countries worldwide. For instance, several medical practitioners canceled their appointments with HIV suspected people in the USA and switched to telehealth appointments to follow the WHO guidelines (Ives, 2020). However, telehealth programs are restricted in the wide range of resources that can be given to the customers (Siwicki, 2020), therefore, PWH may not be able to completely access the services needed for HIV therapy. In addition, many PWH patients may not be able to get access to telehealth services for many reasons, such as limited access to technology and lack of knowledge about telehealth that could hinder their therapy progression.

PWH are more vulnerable group to contract opportunistic infections, such as tuberculosis, toxoplasmosis, pneumonia, etc. (Department of veteran affairs, 2020), than those without immunocompromised systems. HIV-infected people who have suffered from any other disorders may undergo delayed treatment because of COVID-19. This can happen in already taxed healthcare system due to hospital overcrowding. Moreover, PWH who seek out emergency treatment can face a high risk of experiencing COVID-19 among other disorders in the healthcare systems (Collins, 2008).

7. Conclusion and outlook

The occurrence of person-to-person transmission for COVID-19 is increasing, which means that large numbers of cases with second COVID-19 wave of infection are likely to be recorded in the near future. Notably, it has created instability in healthcare systems and more economic losses worldwide (DiMattia et al., 2010). The preventive measurements are enforced globally, and more investigations are underway to identify the origin of infection and to learn more about the characteristics of the virus, route of transmission, severity of the disease, and mechanisms of infection. Since the infection caused by HIV is more prevalent in Asian countries. The rivalry between human immunodeficiency syndrome virus (HIV) and many other illnesses is an appealing problem. Zhu and colleagues reported the first study on the coinfection of HIV and SARS-CoV (Zhu et al., 2020b). They propositioned that persons infected with HIV need to be considered as a vulnerable group for COVID-19. Nonetheless, no robust evidence of any interrelationship between these two viral infections is yet to be identified. Despite the high number of patients infected with HIV as well as the remarkable number of patients with the novel COVID-19 disease, which extends to cover a wide zone in Asia and worldwide. There are very few reports on the co-infection of HIV and SARS-CoV. In addition, antiviral therapeutic drugs are broadly used for treating HIV-infected patients, and these drugs have potential to be used against SARS-CoV-2 (Felber et al., 1990; Savarino et al., 2003). Thus, the patients infected with HIV who are receiving anti-HIV therapeutic drugs might be at a lower risk for COVID-19 compared to the general population. Some antiviral therapeutic drugs, including chloroquine, remdesivir, ribavirin, lopinavir/ritonavir, and now FDA-approved ivermectin and others (summarized Table 3) have the potential to treat patients infected with SARS-CoV-2. At the same time, more clinical trials are required in order to obtain robust data. Also, further studies are urgently required to explore the pathogenicity, mechanisms, and transmission of novel coronavirus.

To obtain a better insight of the novel virus, countries should strive to provide more reliable and accurate data by transparency and sharing of data, and more research studies need to be conducted on the reported cases. Therefore, countries should continue to work towards developing preventive measures to minimize both the transmission and number of infected patients. In addition to unravelling the uncertainty of the mechanisms of viral replication and host cell entry, which will provide the fundamental knowledge for future research into the development of targeted vaccines and antiviral therapeutic drugs. With continuing efforts to curb the widespread transmission of COVID-19 globally, we hope that the novel coronavirus pandemic may alleviate after a few months. In summary, there is an urgent need to develop a new broad-spectrum antiviral therapeutic agent that will be effective to fight against not only the novel respiratory 2019 coronavirus, but also to prepare for a possibly similar virus outbreak in the future. For “If there is any message coming out from the latest outbreaks, it is almost certain that it will happen again.”

Author contributions

Mansab Ali Saleemi, Bilal Ahmad, Khaled Benchoula, Muhammad Sufyan Vohra, and Hing Jian Mea performed the literature search, planned, and wrote the manuscript draft. Pei Pei Chong, Navindra Kumari Palanisamy, and Eng Hwa Wong edited the manuscript and contributed to structure and design. All the authors reviewed and approved the final manuscript draft before submission.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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