HIV vs SARS-CoV-2: Comparison of Structure, Mechanism, and Variants

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Abstract: SARS-CoV-2 and HIV are two of the most widely known viruses in the entire world, with both of them having been studied significantly by the scientific community due to their mechanisms and importance in society. Despite this, the two are very different. This paper delves into and explores the virology of both of these viruses, analyzing the structure, mechanism of entry, mechanism of reproduction, and variants of SARS-CoV-2 and HIV in order to compare and contrast them. Furthermore, this paper analyzes crucial aspects of the two viruses' virology, such as the role of reverse transcriptase in HIV and the role of the receptor binding domain in SARS-CoV-2.

1. Introduction

The human immunodeficiency virus (HIV) is one of the most well-known viruses in the world. Directly targeting the immune system, the symptoms of HIV can result in acquired immunodeficiency syndrome (AIDS). Having been considered a pandemic for several decades, HIV has gained notoriety among the populace. Among the scientific community, however, there has also been significant interest in the virus due to its mechanism. As a part of the Retroviridae family of viruses, HIV has noteworthy importance in gene therapy due to the unusual mechanism shared among retroviruses.[1] Studying retroviruses such as HIV has vastly increased the knowledge of eukaryotic gene expression. While HIV still occupies the minds of the scientific community and the general populace alike, one virus that originated recently has dominated virology and the global media in the last couple of years. SARS-CoV-2, also known as the Coronavirus (after its crown-like structure), or COVID-19 (which means coronavirus disease of 2019), is short for severe acute respiratory system 2.[2] It belongs to a group of viruses that includes MERS (middle east respiratory system), and SARS (severe acute respiratory system).[3] Regardless, the transmissibility of SARS-CoV-2 meant that the magnitude it had on global processes was immense, as a global pandemic was declared rapidly after and has continued since then. The lack of a vaccine at first followed by the creation of variants meant that SARS-CoV-2 remained a significant problem, dominating global media and the lives of people. While both HIV and SARS-CoV-2 have had significant impacts on this world, occupying the minds of the common people and scientists alike, there are crucial differences regarding transmission, symptoms, structure, and the mechanisms of entry and reproduction between the two viruses.

2. Structure of SARS-CoV-2 and HIV

2.1 Structure of SARS-CoV-2

There are 4 major proteins that comprise the SARS-CoV-2 virus, with their names being membrane (M), envelope (E), nucleocapsid (N), and spike (S) proteins.[3] These 4 proteins are shared, or conserved, among other members of the same virus family such as MERS and SARS-CoV-1, further proven by the fact that the genome of SARS-CoV-2 is quite similar to the latter of the 2 relatives, with the nucleotide bases being 80% the same and the amino acid sequence being 94.6% the same.[5] The spike protein is divided into two parts, S1 and S2, and together these form the trimer of the S protein.[5]

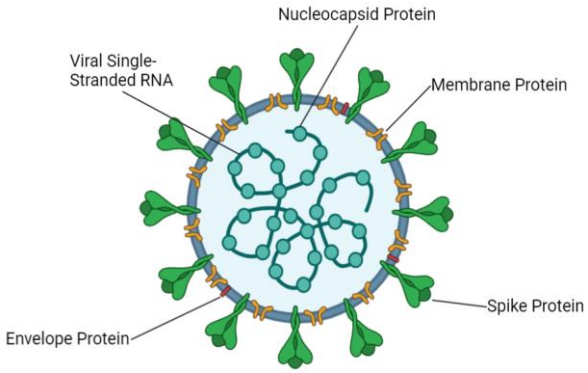

Figure 1: (shown above) This figure shows the structure of SARS-CoV-2 including the 4 key proteins as well as the viral RNA

The S protein has multiple sites, which include: NTD, RBD, CTD1, CTD2, FP, FPPR, HR1, CH, HR2, TM, and CT. The NTD, which stands for the N-terminal domain, has multiple beta sheets which are part of the protein's secondary structure. It is unclear the specific role that it plays.[4] Probably the most important of these sites in the mechanism of infection is the RBD. The RBD which follows the NTD stands for the receptor binding domain. The secondary structure of this section comprises of 5 antiparallel B-pleated sheets, with alpha helices connecting these sheets. The receptor binding domain is the part of the S protein that binds to the ACE2 cell receptor, specifically a loop that wraps around the core of this section. This loop is known as the receptor binding motif or the RBM.[4] The Receptor Binding Motif is also crucial in the mechanism of replication of SARS-CoV-2. Another specialty of the receptor binding domain is that vaccine-released or natural antibodies target the receptor binding domain, in three different sites. These sites, called antigenic sites, are where the antibodies bind. Most of these antibodies use direct competition by detecting the tip of the RBM, resulting in the prevention of the S protein binding to the ACE2 cell receptor.[4] Important to the function of the receptor-binding domain are the conformations that it can have. The receptor-binding domain has two conformations, with the site being in down conformation during formation. During formation, it is against the other 2 RBDs in the trimer and it faces the CTD1 next to it on the sequence, as well as the NTD of the neighboring part of the protomer. While it is in this down formation, it can be targeted. The receptor binding domain changes to up conformation when the CTD1 and the NTD shift away, allowing the site to be fully displayed. Moreover, there is a site known as the “cryptic supersite” which can solely be accessed when the receptor binding domain is in the up conformation.[4] As the premier protein that determines the entry of the virus particle, it is important to understand the structure and function of the S protein.

2.2 Structure of HIV

The HIV virus is comprised of several major components, with those being the glycoproteins, the lipidic membrane, the matrix, the core, and the capsid barrier. The glycoproteins coat the outside of the virion, with there being 2 different types of proteins: gp120 and gp4.[5] These glycoproteins are key to the mechanism of entry. There is a trimer formation with the gp120 proteins being located on the external surface and the gp41 proteins spanning the trimer. The gp120 can be easily shed from the virion, which is a part of the entry mechanism. Under the glycoproteins, there is a lipidic membrane, which plays a large role in the mechanism of replication. Under the lipidic membrane, there is a matrix that is made out of the protein p17.[5] The components involved in the replication of HIV including the ones that are heavily studied are located in the core. The core, which is located under the matrix, is surrounded by a capsid barrier that is made out of p24. The core itself is made out of proteins p7 and p6. In this core, there are 2 single-stranded RNA molecules that also have the reverse transcriptase enzyme located on them.[5] This enzyme is critical during the mechanism of reproduction and is one of the keys to studying retroviruses. The overall structure of the virus is quite unique and is similar to other members of the same family.

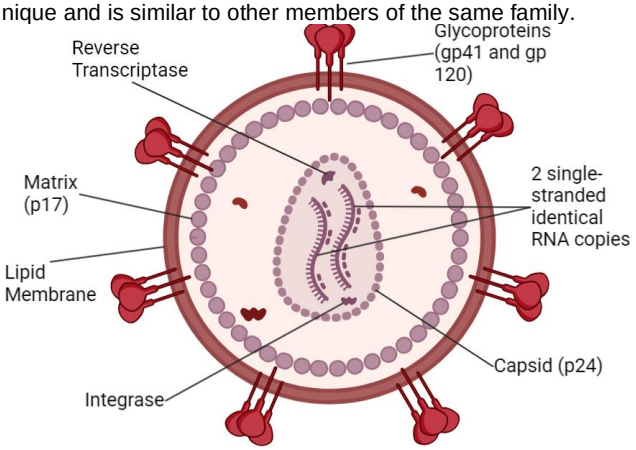

Figure 2: (shown above) This figure shows the structure of HIV including all the major proteins and enzymes involved in the mechanism of entry and reproduction

The retrovirus genome is comprised of two single-stranded RNA located in the core. These two strands are identical copies of each other, and they contain structural genes called *gag*, *pol*, and *env*. These structural genes are conserved among the family, with the *gag* gene encoding the proteins that make up the core and the matrix, the *env* gene encoding the glycoproteins, and the *pol* gene encoding the enzymes that facilitate viral replication, chiefly, reverse transcriptase.[5] However, there are other genes that play a role in replication, even though they are not as well known. These accessory genes and proteins that are also present accelerate the replication process, with examples being the pivotal *tat* gene, the *rev* gene, the vpr protein, the vpu protein, and the nef protein. The *tat* gene is important as it produces the tat protein that promotes the other genes in the HIV genome to be expressed.[5]

2.3 Comparison of Structure

An important similarity that both viruses share is that they both have protein trimers that are on the external membrane, namely the Spike protein for SARS-CoV-2 and the *env* glycoproteins for HIV. They also both have membranes just like all viruses, but one function of the HIV membrane is that its lipid membrane plays a role in replication, picking up proteins from the host cell. They both also have viral RNA, however, there are several crucial differences here. Notably, HIV has 2 identical copies of RNA and it is also well known for enzymes that act upon its RNA such as reverse transcriptase and integrase. However, they still both have key structural proteins that make up the virus, namely env, pol, and gag for HIV and S, M, N, and E for SARS-CoV-2.

3. Mechanism of SARS-CoV-2 and HIV

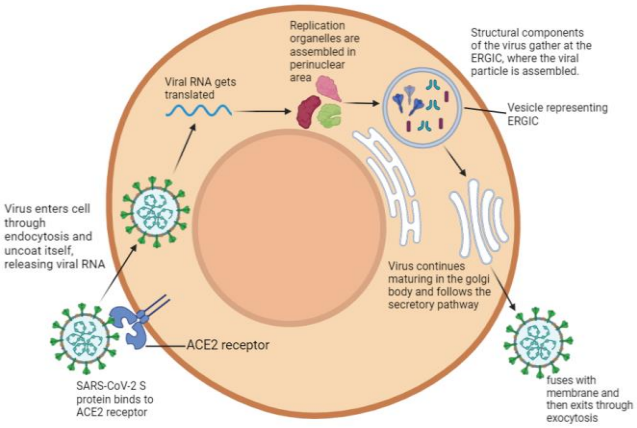

Figure 3: (shown below) This figure depicts the mechanism of SARS-CoV-2 infection, with the binding to the ACE2 receptor, the releasing of RNA, the production of proteins, the assembling and maturing of the virus, and finally exiting of the cell through exocytosis

3.1 Mechanism of SARS-CoV-2

The primary entry receptor that the spike protein binds to on the cell membrane in order to allow virus entry is the Angiotensin-converting enzyme 2 (ACE2).[2] Major conformational changes occur as the spike protein binds to this receptor, with processes such as a site in the S2 subunit being cleaved.[6] The transmembrane protease does this. The S1 subunit is the site that binds to ACE2. Tropism, which is the response the virus has to external stimuli, as well as infectivity are both affected by mutations that occur on the S protein. In order to bind to the ACE2 receptor, they are first detected by cell receptors that activate transcription factors known as NF-kB. As for the types of cells that SARS-CoV-2 infects, it generally binds to ACE2 receptors that are present on epithelial cells in the nasal cavity and respiratory tract, as well as alveolar cells in the lung.[7] Once the Virus enters the host cell's cytoplasm, it releases the viral RNA which is necessary for the replication process. The structure of the viral RNA of SARS-CoV-2 is comprised of a large genome with 5' and 3' ends that are untranslated and instead have secondary structures that are used to synthesize the RNA. There are 2 open reading frames at the 5' end of the viral RNA that have NSFs or non-structural proteins which are used for functions such as modification, and processing RNA.[8] The perinuclear area is the region of the cytosol which is in the nearby proximity of the nucleus. In this region, the replication organelles of SARS-CoV-2 are synthesized, and these organelles are also present in other viruses in the same family. These organelles have several unique properties, such as being surrounded by double membranes, containing viral replication complexes, and taking in and using immune molecules that it sequestered from the cell. These organelles are thought to originate from the Endoplasmic Reticulum because it is in this perinuclear eukaryotic organelle where the proteins that form the virus structure as well as the RNA of the virus are synthesized. The proteins and RNA then get transported to an ER-Golgi intermediate complex that is known as the ERGIC. There, only 4 proteins end up becoming part of the virus, the S (spike), E (envelope), N (nucleocapsid), and M (membrane proteins). Inside the ERGIC complex, the

nucleocapsid protein binds to the RNA molecule in the virus, but the other 3 proteins form the viral membrane. The envelope and membrane proteins help facilitate budding because they work with other virus-associated molecules. Also, the S1 protein binds to the ACE2 cell receptor, but the S2 protein has the important task of helping to facilitate membrane fusion. They then bud into the lumen of the ERGIC, which is the space inside of the ERGIC membrane, and then they follow the secretory pathway of the cell (ERGIC → vesicle → golgi → vesicle → membrane). Finally, the final vesicle then fuses with the fusion peptide in the cell membrane. During the synthesis of the SARS-CoV-2 components, the spike protein subunits undergo a conformation change, specifically the receptor binding domain. While the virion is still being synthesized, the trimer of the S protein has not formed yet and they are still protomers in perfusion. In this state, the receptor binding domain is in down conformation, which is a conformation that prevents ACE2 binding because part of the receptor binding motif is inaccessible. When the receptor binding domain changes conformation, it then exposes the receptor binding motif and allows binding to happen.[4]

3.2 Mechanism of HIV

The proteins that facilitate HIV entry into the cell are gp120 and gp41. These are heterodimeric proteins that are formed in trimers. These result in the virus being recognized by the cell and also help the virus enter.[5] These two proteins, which are env proteins, can bind through multiple different specific mechanisms. One of them gp120, is the one that directly binds to the cell, binding to a glycoprotein called CD4.[9] A conformational change then happens to the virus, and the gp120 changes structure so that it can use a specific domain to bind to chemokine receptors on the cell. These receptors are essential because chemokines help guide and mediate the immune system during problems such as inflammation. When the gp120 binds to both the chemokine and the CD4 it has more excellent stability and the virus is attached a lot stronger than it would have if gp120 had bonded to just one receptor.[5] Then, the gp41 protein penetrates the cell membrane. Then, part of the HIV protein collapses and brings the virus and cell membranes very close together, which allows for the capsid of HIV to enter through fusion with the cell membrane.[9] HIV reproduction begins in the cytoplasm of the host cell, where the core of the HIV virion particle uncoats and releases the 2 identical single-stranded RNA that it contained. Reverse transcriptase, being an enzyme, has active sites, one of which is the ribonuclease H active site. This site, along with another enzyme called integrase converts this RNA into double-stranded DNA that can be inserted into the host genome.[5] Unlike SARS-CoV-2 which directly translates the viral RNA, HIV first goes through the retroviral mechanism by converting the RNA to DNA. This process takes place in the cytoplasm through a process called minus-strand polymerization. A minus is a noncoding strand that is copied by an RNA polymerase in order to produce an mRNA that can be translated. The ribonuclease H active site then breaks down the RNA strand, and the active site of the RNA polymerase then finishes a DNA strand that is complementary to that strand in order to form the double helix structure. Following that process, the integrase uses the DNA and then integrates it into the host genome, by cleaving some nucleotides on the 3' carbon ends of each strand. These ends are colloquially called "sticky ends" and they are pivotal in the integration of the strand. In order for the cell to be infected by these, they have to be active so that the DNA can be expressed through first transcription and then translation. The next step is for the retrovirus DNA to get transcripted and translated, with the regulatory proteins tat and rev being synthesized first, since they can then regulate the production of the remaining necessary genes. There are many other accessory genes that play a large role in the replication of the HIV viruses in addition to the regulatory genes and the genes that code for the structural proteins. The rev protein is crucial as it ensures that the correct gene is being exported as mRNA from the nucleus to the cytoplasm where it gets translated.[5] The vpr protein also plays a pivotal role by arresting the cell cycle in the G2 during HIV replication.[10] This protein also allows the reverse transcriptase enzyme to access the nucleus in non-dividing cells, which facilitates RNA-to-DNA conversion.[5] The vpu protein, which ensures that the virus particle is released more efficiently, and the vif protein, which ensures that any viruses that are produced in the cell are infective, are also critical to replication.[10] Finally, another important accessory gene is the nef protein which has functions such as facilitating signal transduction and virus budding during the end of the replication cycle.[5] Both vpu and nef proteins function in tandem with the CD4 receptor.[10] The *tat* gene then binds to a site called TAR which stands for transactivation response element present at the beginning of the internuclear RNA sequence. This allows for longer sequences of mRNA to be transcribed. It also inhibits regulatory protein production which is necessary to increase the maturity of the virus. Genes that make up the HIV cell such as the *pol*, *gag*, and *env* genes are now being transcribed. The *env* gene, in particular, plays an important role due to its production of the HIV glycoproteins gp120 and gp41. These two glycoproteins are formed when HIV-1 protease cleaves gp160, which is the protein that env codes for. HIV-1 protease then uses a precursor molecule in order to derive both the gag and pol proteins, which are subsequently split into the p24, p17, p9, and p7 proteins. Then, the 2 viral identical single-strand RNAs assemble along with the replication enzymes like reverse transcriptase while the capsid forms, surrounding them. This virus particle then travels toward the surface, budding through the membrane. This is where the particle acquires an envelope, becoming filled with components of the cell's plasma membrane such as cholesterol, phospholipids, and the host cell's membrane proteins as well. In a type of cell called T-lymphocytes, the budding of the virus particle occurs directly at the plasma membrane of the host, but in other types, namely monocytes and macrophages, the budding is different. In these cells, vacuoles present in the cytoplasm of the cell collect these budding viruses and then release them externally.[5]

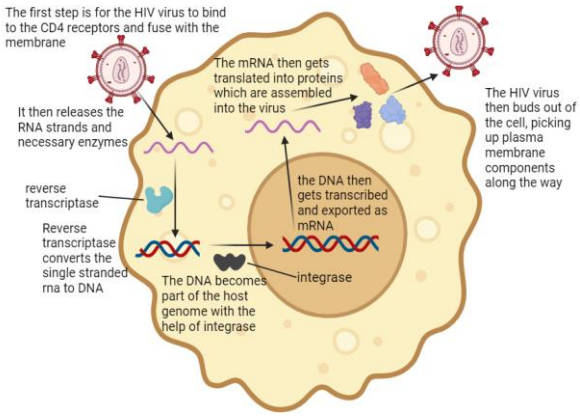

Figure 4: (shown below) This figure shows the process of HIV infection of a cell, with the entry, viral RNA conversion to DNA, integration, transcription, translation, and finally the budding.

3.3 Comparison of Mechanism

Perhaps the biggest difference between the two viruses lie here. While both of them bind to a receptor on the cell surface, the SARs-CoV-2 virion actually enters the cell through an endosome[8], while HIV fuses with the membrane and releases the contents of its core into the cell. This means that the uncoating of both viruses, where they release the necessary components for replication into the cytoplasm, happens during different stages. Also, a pivotal difference is that HIV undergoes the retroviral method of replication, where the viral RNA is first converted into DNA, integrated into the host genome, and then transcribed and

translated. On the other hand, SARS-CoV-2 follows the more generic method of releasing viral RNA, which then gets translated, forming the necessary proteins. Both viruses have several genes that are involved for regulation rather than producing structural proteins. Also, both viruses include components from the cell during replication, with SARS-CoV-2 taking in immune cells and HIV taking in membrane proteins. They both then undergo exocytosis and exit the cell.

4. SARS-CoV-2 and HIV Variants

4.1 SARS-CoV-2 Variants

Compared to HIV or even influenza, the rate of mutations of the SARS-CoV-2 virus is minimal, with there being 10-4 nucleotide substitutions per site every year. However, due to the unusually high transmission rate of this novel virus, not only is there a higher probability of mutations being present, but the mutations can spread far more easily. There are two types of prominent variants as per the Technical Advisory Group on Virus Evolution (TAG-VE) a group that works with the World Health Organization to help monitor and classify COVID-19 variants. The first type is a variant of interest, which is classified by having genetic changes that can affect crucial characteristics, resulting in increased regional transmission. The more severe version, a variant of concern, presents an increased health risk through the decrease in effectiveness that treatments have on it, in addition to having significant genetic changes in characteristics such as transmissibility, symptoms, and epidemiology.[11] There are several prominent and important variants of SARS-CoV-2. The alpha variant has several deletions and mutations in the spike protein. One of these in particular, the N501Y substitution, is not only present in other variants, but it is significant in that it results in a 4 times greater affinity for the cell receptor ACE2. This hampers the dissociation of the receptor binding domain from the cell receptor and as a result, increases transmissibility. Primarily, it was prevalent in the United Kingdom in early 2021 and decreased the efficiency of the COVID-19 vaccine with experiments showing that the vaccine did not prevent infection, although the magnitude of the disease was still reduced. The Beta variant also has mutations on the spike protein including the N501Y substitution, as well as the K417N and E484K substitutions that can be found in other variants as well. Once again, there is a decreased effectiveness of vaccines with the rate of transmission is increased despite vaccination. Displaying the ubiquitousness of the pandemic, the Beta variant was first identified in South Africa, across the world from the United Kingdom and China.[11] Similarly, the Delta variant was discovered in India but then became the most prominent variant in the world until the Omicron variant.[12] The massive increase in the transmissibility even compared to the other variants of SARS-CoV-2 in addition to its increased rate of replication resulted in this. Generally, however, the effectiveness of major vaccine brands did not decrease significantly. In January 2021, another variant, the gamma variant, was first noticed in Japan. Differing greatly from the original virus, it contains 12 mutations sharing the aforementioned N501Y, E484K, and K417T with the Beta variant among other variants. There is increased transmission of the variant as a result, primarily in Brazil, where the spread was especially sudden. Finally, In November of 2021 in the country of Botswana, the infamous Omicron variant emerged, which has over 30 mutations in the spike protein including roughly 15 of them being in the receptor-binding domain. It also shares the aforementioned 3 substitutions that are also in the gamma and beta variants. In order to neutralize the omicron variant, the 3rd dose of the commonly utilized Pfizer and Moderna vaccines is necessary, with there being little effectiveness in the 1st and 2nd doses of the vaccine. There is also a massive increase in affinity, with 2 times more even when compared to the already highly transmissible Delta variant. Despite this, the omicron variant is mild compared to other variants as indicated by the lack of a mortality rate increase despite the increase in the number of infections in certain countries.[11]

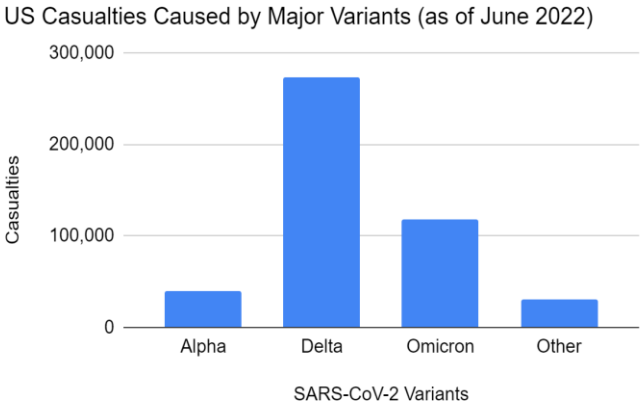

Figure 5: The graph below shows the casualties caused by certain variants in the US as of June 2022[13]. The 3 major variants shown, despite not originating from the US, caused the majority of variant-related casualties. Still, there were other variants that caused a significant amount of casualties.

4.2 HIV Variants

The variability of HIV is one of the major reasons why HIV has been so persistent to this day, as it allows the virus to bypass host immunity and treatments. There are 3 unique reasons why HIV has so much variability. First of all, reverse transcriptase is quite “error-prone” which means that new mutations arise that can change the genome of HIV. Secondly, the viral replication process of HIV is extremely rapid, generating roughly 1010 new HIV cells in the individual, which once again allows for a quicker rate of mutation and thus genetic changes. Finally, inside the same individual, recombination can occur between multiple variants of HIV viruses can result in the genome of a virus changing. There are 2 major HIV types, HIV-1 and HIV-2, which have been determined based on how similar the genomes have been between different viruses. Both of these types have multiple different divisions and subdivisions, with HIV-1 having 3 groups designated as M (Major), O (outlier), and N (non-M/non-O). These are further divided into 9 clades/subtypes that are labeled from A to K and have their own sub-subtypes as well. These are a result of a phenomenon where viruses of two different HIV subtypes infect the same cell and share parts of their genetic material through a process similar to sexual reproduction, which has led the process to be colloquially known as “viral sex.” While a lot of these new strains of HIV cannot replicate, some can be transmitted. The ones that can be transmitted are known as CRFs which stand for circulating recombinant forms. Similarly, HIV-2 can also be divided into major groups and subtypes.[5]

4.2.1 HIV Variant Distribution

The distribution of these variants across the world is uneven, for example, the O and N groups of HIV-1 are generally limited in the region of Gabon, Cameroon, and other countries that are in that region. Another example of this uneven distribution would be Unique Recombinant Forms, or URFs, which are viruses that have been formed through recombination or “viral sex” of multiple different HIV viruses but have not been transmitted past the original location. The massive variability present within this genetically diverse virus has led to a very non-homogenous composition of HIV viruses in places such as Africa which contains numerous subtypes. In fact, even within the subtypes of HIV-1, the viruses vary substantially. Sub-Saharan Africa in

particular contains every single HIV-1 variant, with A and C being the most common, however. HIV-2, the other variant of HIV originated in West Africa but it has since then spread to regions such as India and Portugal, as well as other regions in Europe. Recombinant forms such as CRFs and URFs are becoming more prevalent and ubiquitous, with places such as Argentina, Brazil, East Europe, and Southeast Asia containing different variations of CRFs.[5]

4.3 Comparison of Variants

Both SARS-CoV-2 and HIV are well-known for their variants. For HIV, the unusually high variability allows for there to be many different groups, subtypes, and sub-subtypes. On the other hand, SARS-CoV-2 also has a lot of variants due to its high transmissibility. This is also a major difference between the variants of the two. SARS-CoV-2 has variants that quickly traverse the entire globe, whereas HIV variants mostly occupy a couple of specific regions. There are still SARS-CoV-2 variants that only occupy a specific region, but large variants such as Delta and Omicron generally spread across the world, even though SARS-CoV-2 has emerged a lot more recently than HIV. HIV is also unusual due to its possession of recombinant forms that are formed through “viral sex,” something that is not present in SARS-CoV-2.

Conclusion

Despite being two of the most well-known viruses, the differences between the two are vast and varied. Looking at the structure, HIV is quite different from SARS-CoV-2 due to its possession of the unique reverse transcriptase and lipidic membrane. However, they both have similarities in their mechanism of entry, which both involve detecting a cellular receptor and binding through a projection of their viral membrane, which would be the spike protein for SARS-CoV-2 and the glycoproteins for HIV. One major difference in entry is that SARS-CoV-2 targets the cells that line the inner lungs and other organs, while HIV targets immune system cells such as T-lymphocytes, macrophages, and monocytes. Furthermore, HIV also fuses with the cell membrane and releases its contents inward. Perhaps the greatest difference between the 2 viruses is in their mechanism of replication. SARS-CoV-2 utilizes the perinuclear area to synthesize replication organelles through the more common method of viral RNA being translated to create these viral proteins, before manufacturing the actual virion in the ER-Golgi intermediate complex before exiting the cell through the secretory pathway. On the other hand, HIV, following the more unconventional and uncommon retroviral mechanism of reproduction, has the extra step of converting its own RNA to DNA using reverse transcriptase and then integrating the DNA into the host genome so that it can be transcribed and translated to create all the proteins necessary for HIV replication. Only then are the proteins modified to create the HIV virus, which buds through the cell membrane. A major similarity between the 2 viruses is that they both have a substantial amount of variants, with a massive rate of mutations in HIV corresponding with a monumental transmissibility in SARS-CoV-2. Even here, however, there are major differences. For HIV, there is no clear distinction in which variant is more common other than geographical differences. There is also the unusual capability of HIV subtypes to recombine and create new variants in the process, something that SARS-CoV-2 is not known to do. On the other hand, SARS-CoV-2 variants are known for their increased resistance to healthcare as well as large increases in the rates of transmission. As a result, unlike HIV variants, SARS-CoV-2 variants rapidly spread across the world and often result in massive spikes in infection rates. Indubitably, however, despite all the differences, one similarity remains clear: The assertion that both of these viruses are some of the most pivotal viruses that have ever affected humans, not only in the scientific community but also the entire world.

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