

A Review of Human Immunodeficiency Virus

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Abstract

Human immunodeficiency virus, also referred to as HIV, is a devastating virus which has infected millions. Characterized as a retrovirus, HIV has an RNA genome, which is reverse transcribed into DNA upon entry into the host cell. HIV primarily affects CD4⁺ T cells and is diagnosed by the significant reduction of CD4⁺ T cells. While no cure has been discovered yet, antiretroviral therapy (ART) has been demonstrated as an effective treatment option. In the progression of HIV, additional HIV-associated diseases may arise, including HIV-associated psoriasis and sensory neuropathy. In addition to the use of ART, clinicians often prescribe opioids to manage the chronic pain experienced by patients with HIV. However, studies have demonstrated the immunosuppressant properties of opioids, which enhance HIV infection and must therefore be taken into consideration in the treatment of HIV.

Keywords: human immunodeficiency virus, HIV, antiretroviral therapy, immunosuppression, sub-Saharan Africa, opioid management

Introduction

Human immunodeficiency virus (HIV) is a devastating disease that has infected millions worldwide and has induced high mortality rates. Tragically, 37.9 million people were infected with HIV in 2018, 1.7 million of whom were children under 15 years old. While HIV may present in individuals as HIV-1 or HIV-2, HIV-1 is more commonly diagnosed. Since its discovery in the early 1980s, HIV has been extensively researched to uncover the underlying molecular mechanisms of this disease. While the discovery of a definitive cure has progressed slowly, the spread of this virus has increased rapidly. Progress on the treatment includes first, a comprehensive understanding of the pathophysiology of HIV, with emphasis on the viral structure, modes of entry, and primary infection of T cells, second, an investigation of the role of opioids in immunosuppression and subsequent enhancement of HIV infection and third, an examination of the role of clinicians in treating HIV patients, especially those at risk for opioid abuse.

Epidemiology

While many cases arise each year in the United States, HIV is most prevalent in sub-Saharan Africa, where 85% of HIV cases exist (Williams et al., 2017). In more economically disadvantaged areas, treatment options may be scarce, significantly affecting the infected individual's chance of survival. Such is true in areas like sub-Saharan Africa, where a study conducted in 2015 revealed that 6.5 to 19 million people were infected with HIV, and 330,000 to 470,000 people experienced HIV-related deaths (Nansseu and Bigna, 2017). These statistics demonstrate the need for increased accessibility to antiretroviral therapy and production of more cost-effective versions of antiretroviral therapy (ART) (Zulfiqar et al., 2017).

Pathophysiology

HIV-1 and HIV-2

Infection may be caused by type 1 or type 2 HIV. Though they are distinct from one another, both share certain biological and genetic characteristics. HIV-1 is thought to have originated from the simian immunodeficiency virus (SIV), which infected African chimpanzees, while HIV-2 may have originated from SIV-infecting sooty mangabeys (Owen et al., 2013). Interestingly, while HIV-1 infections are global, HIV-2 infections are found primarily in West Africa, parts of India, and some former Portuguese colonies including Angola, Mozambique, and Brazil (Vidya Vijayan et al., 2017). Due to the global prevalence of HIV-1, primarily the specifics of this strain will be examined.

HIV-1 Structure

Analysis of the viral genome has revealed key structures that aid in the infection of host cells. Within the genome, three genes code for structural features, while six additional genes code for accessory and regulatory enzymes (See Figure 1) (Owen et al., 2013). Encoded by the *ENV* gene, the HIV-1 envelope glycoprotein is the receptor that binds to CD4⁺ on host T helper cells and facilitates subsequent fusion with CD4⁺ T cells. Proteolytic cleavage or dissociation of the trimeric glycoprotein forms gp120 and gp41 heterodimers, which are crucial for proper attachment and fusion with the host cell membrane. Significantly, the ENV glycoprotein is the only target for neutralizing antibodies (Ward and Wilson, 2015).

A second structural gene is *GAG*, which encodes a main protein of HIV-1 involved in particle packaging. As a polyprotein, GAG contains three conserved domains: a matrix (MA), capsid (CA), and nucleocapsid (NC). GAG plays a major role in the assembly of virion particles

through GAG-GAG, GAG-membrane, and GAG-RNA interactions. Furthermore, the production of virion particles produced is dependent on the level of *GAG* expressed. Finally, packaging assembly requires recognition of HIV-1 RNA by HIV-1 GAG polyprotein. This is dependent on the presence of a packaging signal within the HIV-1 genome (Dilley et al., 2017).

The final identified key structural gene is *POL*, which encodes proteins involved in replication including protease (PR), integrase (IN), and reverse transcriptase (RT) (Nagata et al., 2017). HIV-1 PR plays a primary role in cleaving HIV-1 polyproteins to form mature proteins and produce more virion particles (Rögnvaldsson et al., 2015). HIV-1 RT is responsible for the conversion of HIV-1 single-stranded RNA into double-stranded DNA form (Sluis-Cremer et al., 2004). Formulating treatments to target these proteins may be challenging due to the high incidence of amino acid variability within each of these proteins (Rhee et al., 2016).

Six additional genes encode associated, supporting proteins. Of these six, two regulatory proteins are encoded by *TAT* and *REV*. A recent study on the role of TAT revealed its strong immunosuppressive qualities and ability to cross the blood-brain barrier (BBB). Additionally, TAT was shown to terminate the apoptosis pathways through induced expression of Bcl-2 protein. Significantly, increased expression of Bcl-2 offers an additional way to inhibit apoptosis apart from suppressing caspase-3. Furthermore, TAT inhibits CD4⁺ and CD8⁺ maturation through the interruption of specific cytokine expression within the T cells (Karampoor et al., 2020). HIV-1 REV also plays a regulatory role in the nuclear export of unspliced and partially spliced transcripts. Binding to a 351-nucleotide region identified as the REV response element (RRE), REV tags the viral transcripts with nuclear export factor Crm1. The export of these

transcripts is necessary for the formation of viral particles and production of structural proteins (Watts et al., 2018).

The accessory proteins encoded by *NEF*, *VIF*, *VPU*, and *VPR* are important in the infection process of HIV-1. During this process, the protein NEF targets host transmembrane proteins SERINC5 and SERINC3 and redirects them to a Rab7-positive endosomal compartment. This prevents SERINC5 and SERINC3 incorporation into virion particles, which normally disables particle entry into additional host cells (Rosa et al., 2015).

Identified as an intrinsically disordered protein (IDP), VIF is essential for viral replication in non-permissive cells. In the absence of VIF, APOBEC3G antiviral protein and other members of the APOBEC family may be incorporated in the HIV-1 virions, where they function as cytidine deaminases. Here, they replace cytidines (C) with uridines (U) in the reverse transcript strands. These mutations then translate from guanosines (G) to adenosines (A) in the transcribed double-stranded DNA, forming hypermutations. VIF binds to antiviral proteins of the APOBEC family to prevent this viral genome replication disruption through hypermutations. (Chan et al., 2018; Goila-Gaur and Strebel, 2008; Malim, 2006).

VPU plays a major role in the downregulation of host cell proteins, including T cell immunoglobulin and mucin domain-containing protein (Tim-3) (Cole and Sharpe, 2019; Prévost et al., 2020). Furthermore, VPR is required for replication in macrophages and has been demonstrated to accelerate viral replication. VPR contributes to the progression of HIV-1 infection and impacts the host cell in a variety of ways, including negative alteration of the host cell's energy metabolism, oxidation, and proteasome activities (González, 2017).

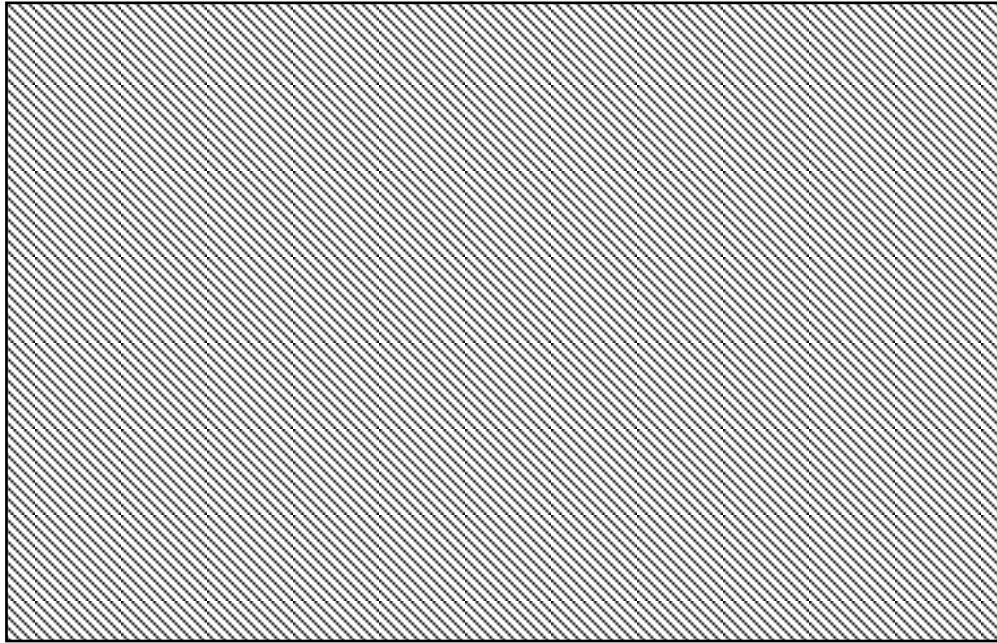


Figure 1. HIV-1 Encoded Proteins.

The organization of the HIV-1 genome and the expression of HIV-1 proteins are pictured. Primary structural proteins include GAG, POL, and ENV. Accessory proteins include VIF, VPR, VPU, and NEF, while regulatory proteins include REV and TAT. **A**, pictured is the 5' to 3' reading frame for all major structural, accessory, and regulatory proteins encoded in DNA form. **B**, shown here is the HIV-1 genome in RNA form, requiring reverse-transcriptase activity. **C**, shown here are the transcripts for HIV-1 proteins which are either RRE-REV independent or dependent. Starring represents where splicing occurs. Figure obtained from Kirchhoff, Frank et al., 2018.

Cell Types and Receptors Targeted by HIV

The immune system constitutes an irreplaceable defense system within the body to combat infection and disease. As its name implies, HIV greatly impairs the immune system. The discovery of the viral genome being stored in the form of RNA rather than DNA led to the classification of HIV as a retrovirus. Previously, the only virus known to be a retrovirus was human T-cell lymphotropic virus I (HTLV-1). Thus, this was a significant discovery (Owen et al., 2013, p. 608).

As a retrovirus, HIV-1 primarily targets CD4 receptors on T lymphocytes upon entry to the body (Doitsh and Greene, 2016). CD4⁺ T cells constitute approximately 65% of the T cell population, while CD8⁺ T cells form the remainder (Ma et al., 2018). Comprised of four immunoglobulin-like domains and one ectodomain, the CD4 receptor is vital in the activation process of T cells. However, CD4 receptors also negatively contribute to HIV-1 infection (Chen, 2019). Additional targeting of monocytes and macrophages with CD68⁺ receptors occurs within the spleen, liver, brain, lungs, bone marrow, and lymph nodes. Dendritic cells within lymphoid germinal centers and upon lymphoepithelial surfaces are also susceptible to HIV targeting (Lucas and Nelson, 2015).

Targeting occurs in the fusion process, whereby the virus enters the host cell. The process involves the approach of two membranes and subsequent overcoming of kinetic barriers for fusion to successfully occur. In most cases of fusion, the HIV-1 envelope glycoprotein initiates virion and host cell membrane attachment and facilitates subsequent fusion. The glycoprotein's interaction with the CD4 receptor and, at times, additional coreceptors CCR5 or CXCR4, leads to entry of HIV into the host cell (Chen, 2019).

Replicative Life Cycle of HIV within Host Cells

Proliferation of the HIV infection depends on successful integration of the viral genome into the cellular genome (See Figure 2). Following the fusion of the viral and cellular membranes, the virus is released into the cell's cytoplasm. The invading RNA is then transcribed into DNA through the activity of viral reverse transcriptase. In order to pass through the nuclear pore complex (NPC) and into the nucleus, a pre-integration complex (PIC) containing the viral

DNA, viral integrase, and capsid proteins must first form. This entry into the nucleus is also dependent on the lymphocyte's stage in the cell division cycle (Lusic and Siliciano, 2017).

Areas with greater gene concentration and activity are targeted for the integration of viral DNA into the normal genome. While many factors influence the positioning of the viral genome's integration, the integration process depends primarily upon the performance of integrase, which is encoded by the *POL* gene and has a central catalytic core domain (CCD) that is highly conserved in retroviral integrase proteins. Integrase performs specific functions of viral DNA 3'-end processing and strand transfer reactions. Additional influencers include sequence specificity, chromatin structure, and cellular tethering factors (Lusic and Siliciano, 2017).

The viral invasion is directed towards lymphocytes with permissive nuclear environments rather than nuclear environments in a resting state. In resting CD4+ T cells, the viral genome undergoes transcriptional silencing after integration. This creates a latent viral reservoir in inactivated cells, which contributes to the challenge of eradication. Currently, the process of viral integration into the host genome remains the only step within the nucleus that may be targeted and inhibited by pharmacological treatment. A better understanding of the mechanism of viral integration could potentially lead to treatment improved in effectiveness and efficiency (Lusic and Siliciano, 2017).

Following integration, transcription of the viral genome requires the binding of TAT to the transacting response (TAR) element. TAT initiates the transcription of full-length HIV-1 transcripts, as well as over 25 additional mRNAs produced from splicing. These splicing variations encode additional HIV proteins required for the spread of infection. The transcription of the viral genome allows for the export of RNA transcript from the nucleus, where translation

occurs and new virion particles may be assembled, packaged, and released to infect additional host cells (Kirchhoff, Frank et al., 2018).

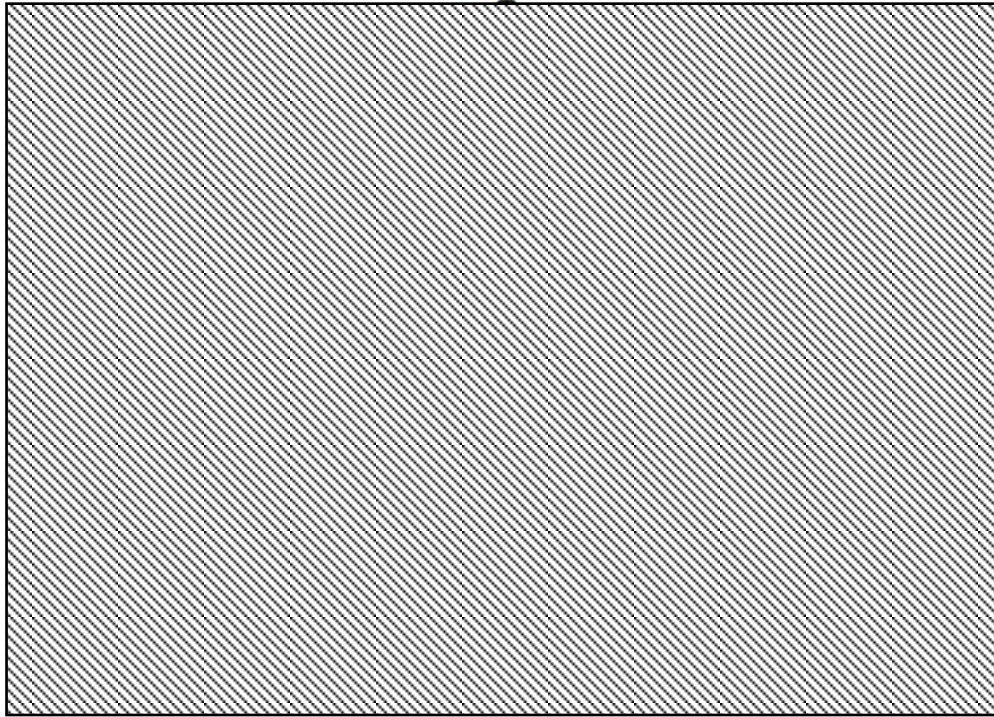


Figure 2. HIV-1 Replicative Life Cycle.

The replicative life cycle of HIV-1 involves multiple stages and relies on protein formation and activity. The virus enters the host cell by binding chemoreceptors CCR5 or CXCR4 (not pictured). Fusion of the virus membrane with host cell membrane leads to viral entry and subsequent replication and infection through the stages of reverse transcription activity, nuclear import, integration, transcription, RNA export, translation, assembly, budding, and maturation. Figure obtained from Kirchhoff, Frank et al., 2018.

Host Cell Response

The cellular response initiated upon HIV infection depends on the location and state of the CD4 T lymphocytes. Two primary modes of cellular response leading to programmed cell death have been identified: apoptosis initiated by caspase-3 and pyroptosis initiated by caspase-2 (See Fig. 3). Apoptosis occurs in permissive CD4 T lymphocytes, which constitute 5% of the CD4 T lymphocyte population. In contrast, pyroptosis, a more intense form of programmed cell

death leading to inflammation, occurs in the resting, nonpermissive CD4 T lymphocytes, which comprise approximately 95% of the CD4 T lymphocyte density (Doitsh & Greene, 2016).

The cellular responses of apoptosis and pyroptosis lead to a drastic reduction of T lymphocytes. Significantly, this depletion of CD4 T lymphocytes has been identified as the causative link to the progression towards acquired immune deficiency syndrome (AIDS) (Ma et al., 2018). Notably, however, the pathway of pyroptosis cannot occur in all resting CD4 T lymphocytes, specifically those circulating in the blood. In this case, the virus remains in the dormant lymphocytes, causing the viral load to increase over time (Doitsh & Greene, 2016).

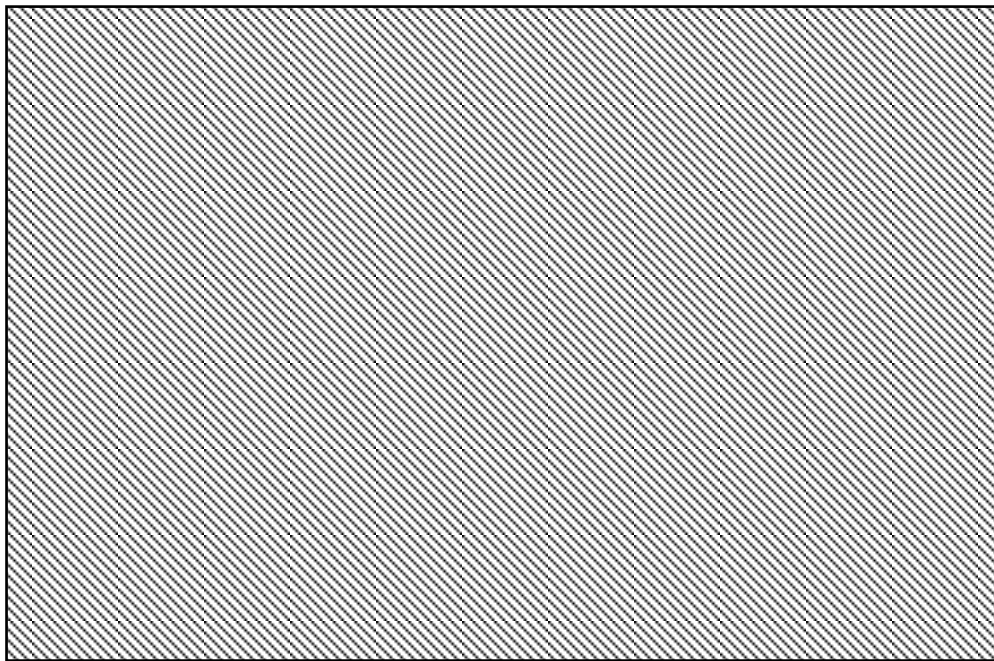


Figure 3. Side-by-Side Comparison of Cellular Death in Non-Permissive and Permissive CD4 T cells.

Pictured are the two alternative pathways for host cell response. In infected non-permissive CD4 T cells, caspase-1 is activated, initiating pyroptosis. In contrast, caspase-3 is activated, initiating apoptosis in infected permissive CD4 T cells. Figure obtained from Doitsh & Greene, 2016.

Clinical Presentation

Medical Indications and Symptoms

The progression of HIV infection occurs in three main stages. The acute or primary stage begins immediately after infection. As the infection spreads, the viral load, or number of virions, rapidly increases. During this stage, the anti-HIV-1 antibodies are not yet detectable, as seroconversion may take months to develop. Within 2 to 4 weeks of exposure, infected individuals may experience flu-like symptoms. Lymphadenopathy and overall malaise are common as well (Owen et al., 2013).

As the infection progresses into the second stage, an asymptomatic period occurs. While the individual may experience no outward symptoms, a vicious internal response is occurring. The immune system activates antibodies and cytotoxic CD8⁺ T lymphocytes that help combat viral replication and reduce the viral load. However, a gradual decline in CD4⁺ T cells persists. Furthermore, the high replication rate of virus in infected CD4⁺ T cells continues, causing up to 10⁹ virions to be released per day. Over time, the rate of viral replication and virion release combined with persistent CD4⁺ depletion may overcome the immune system's defense. The set point, measured by the level of viral load 6 months after infection, is often an indicator of the virus's progression and an individual's prognosis.

Entry into the third stage indicates the progression to AIDS. This occurs in most cases where HIV-1 goes untreated. The diagnosis of AIDS requires the meeting of four criteria. First, antibodies or viral RNA are detected in the blood, indicating HIV-1 infection. Second, low concentrations of CD4⁺ T cells (<200 cells/ul of blood) are measured. Following these two factors, infected individuals may experience delayed or diminished immune responses to other

infections. Finally, the individuals may develop certain opportunistic infections, such as a *Candida albicans* infection, characterized by mouth sores; vulvovaginal yeast infection, experienced by women; or *Pneumocystis carinii* infection in the lungs, identified by a hacking cough. Entry into late-stage AIDS may lead to infections such as tuberculosis, pneumonia, or severe wasting diarrhea.

HIV-Associated Disease Complications

HIV-associated psoriasis. Skin disorders are also commonly experienced by individuals infected with HIV. One such disorder is psoriasis, which is a chronic autoimmune disease that causes skin inflammation. The severity of psoriasis may range from mild to extremely severe and often corresponds to the degree of immunosuppression. Symptoms of psoriasis are often presented in a clinical dermatological setting and may indicate the onset of HIV (Ceccarelli et al., 2019).

Psoriasis may present in numerous forms. This includes plaque psoriasis, nail psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, and rupioid psoriasis. Of these variations, inverse psoriasis, or sebopsoriasis, is the most common in HIV-infected populations. Lesions, appearing greasy and crusty, are mainly found under the armpits, around the breasts, and in the groin and genital area. Guttate psoriasis is another common form and appears primarily in children and young adults. Affected skin is normally in the region of the arms, legs, scalp, and trunk in the form of small droplet-shaped scaly lesions. The third most prevalent form in people with HIV is erythrodermic psoriasis. Characterizations of this type include desquamate areas of skin as well as itching and burning (Ceccarelli et al., 2019).

While the exact mechanism by which HIV infection triggers psoriasis remains unknown, a correlation between increased severity of psoriasis inflammation and decreased concentration of CD4⁺ T cells is suspected. In cases of HIV infection, CD4⁺ T helper 1 (Th1) cells are activated. Cells are also stimulated to secrete interleukin (IL)-23, IL-12, interferon (IFN) gamma and tumor necrosis factor (TNF) alpha. As the level of CD4⁺ T cells decreases, the ratio of CD4⁺ to CD8⁺ T cells becomes significantly unbalanced. As such, CD8⁺ T cells, specifically memory CD8⁺ T cells, are thought to majorly contribute to the formation of skin lesions through their large presence in dermis and epidermis of these lesions and stimulation of pro-inflammatory cytokines, such as IL-17, IL-22, IFN gamma, and TNF alpha. Significantly, this has also been linked to triggering keratinocyte proliferation. Additional studies indicate instances where HIV-encoded Nef protein functions as a superantigen, while other studies suggest that HIV-encoded Tat directly stimulates epidermal and endothelial cell production (Ceccarelli et al., 2019).

Treatment for this disease complication requires a non-traditional approach, as conventional treatments involving immunosuppressants must be avoided as much as possible. In the mild to moderate cases of psoriasis, combined antiretroviral treatment (cART) has proven effective. This involves the use of topical medications such as calcipotriene, corticosteroids, and tazarotene in conjunction with ART. In moderate to severe cases, ultraviolet radiation (UV) is used as a first line treatment option, while oral retinoids are used as a second line alternative (Ceccarelli et al., 2019).

HIV-associated sensory neuropathy. As time has progressed, HIV-associated sensory neuropathy (HIV-SN) has been observed as a frequent disease complication in HIV-infected populations. Significantly, 30-60% of HIV-infected people experience this. HIV-SN is

characterized by pain originating in the distal lower extremities, which may radiate throughout the body to more proximal areas. In more severe cases, the upper extremities may also be affected. Individuals with HIV-SN have also noted fatigue, sleep disturbance, and depression due to chronic pain. As this pain is hard to assuage, affected individuals often experience negative changes in their quality of life (Kuo et al., 2019).

This chronic condition is thought to have two possible causes. First, distal axonal degeneration is thought to be caused by the HIV-encoded glycoprotein gp120. In one investigation of the link between HIV-1 and infection-induced neuropathy, gp120 was demonstrated to significantly damage sensory axons. Axonal damage could occur via two separate pathways: cell apoptosis in the cell body compartment and local caspase activation in the axon. In addition, it was determined that 63% of axons exhibited the chemokine CCR5 receptor while 94% expressed the CXCR4 receptor. Further testing revealed the presence of these receptors on axons enabled gp-120 binding, which caused axonal damage. The second possible cause of axonal damage has been linked to the antiretroviral agents. ART specifically involving viral reverse-transcriptase inhibitors is suspected to unintentionally induce damage in axons. In the conclusion of the study, the development of chemokine inhibitors to prevent initial HIV entry were suggested as a potential aid in combatting the effects of HIV-1 in its progression towards AIDS (Melli et al., 2006).

Diagnosis

Over time, diagnostic techniques have increased in sophistication and sensitivity. Diagnosis techniques include PCR or viral load, P24 test, first/second/third generation Antibody (Ab) tests, fourth generation Antibody/Antigen (Ab/Ag) tests, Western blot tests, and rapid

testing through capillary blood, urine, or oral secretion samples (See Table 1). With advancement of diagnostic techniques and equipment, the HIV antibody can now be detected within only one to two weeks after infection. However, the P24 test may be used to detect P24 antigenic protein, a protein produced by HIV *GAG* gene that forms a major part of the viral core, and confirm HIV infection before antibodies become detectable (Bystryak and Acharya, 2016; Zulfiqar et al., 2017). Circumstances, accessibility, and timeframe factors all contribute to the specific test used for each patient. An early diagnosis is pertinent for prevention of further transmission and the effectiveness of ART treatment.

Type of Test	Detection of DNA/RNA	Detection of Antigen	Detection of Antibody
PCR or viral load	Y	N	N
P24 test	N	Y	N
4 th generation Ag/Ab tests	N	Y	N
Duo, Combo/Combi, etc.	Y	Y	Y
1 st /2 nd /3 rd generation tests	N	N	Y
Rapid tests (finger prick/oral swab)	N	N	Y
Western blots look for Ab to specific HIV proteins	N	N	Y

Table 1. Tests used in the Diagnosis of HIV-1.

Listed above are different tests used in the diagnosis of HIV-1. Tests involving the detection of antibodies are most commonly used. Tests may be chosen based on availability, timeframe and economic factors, and the specific needs of each patient. Table data obtained from Zulfiqar et al., 2017.

Treatment with Antiretroviral Therapy

Since the discovery of HIV around forty years ago, treatment options have dramatically improved. Currently, the best treatment option exists in the form of antiretroviral therapy, which

exists as a combination therapy. The standard combination includes three substances: two nucleoside reverse transcriptase inhibitors (NRTI) with an integrase inhibitor (INI), boosted protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNTRI), or entry inhibitor. NRTIs effectively inhibit viral reverse transcriptase proteins and prevent the translation of single-stranded RNA into proviral double-stranded DNA. Abacavir or tenofovir are normally chosen as the first NRTI, with indistinguishable differences in efficacy. However, abacavir may only be administered in cases where human leukocyte antigen HLA-B 5701 is negative in order to prevent occurrences of hypersensitivity reaction, while tenofovir is the favored choice in the presence of hepatitis B. Lamivudine (3TC) or emtricitabine (FTC) is normally selected as the second NRTI. No significant differences in efficacy have been detected (Lehmann et al., 2019).

Typically recommended as the third substance, an integrase inhibitor prevents the insertion of viral DNA into the human genome within host cells. Alternatively, PI prevents HIV protease from producing cleaved subunits of GAG-POL protein and thereby impedes the production of viral-containing particles. Another alternative would include a NNRTI, which functions similarly to NRTIs. Finally, entry inhibitors may be used in the combination of ART. Entry inhibitors may function in a variety of ways, depending on the type used. This includes types that prevent viral entry by coating protein gp120 and CD4 receptor, binding coreceptors CCR5 or CXCR4, or fusing the virus and cell with the subcutaneously administered fusion inhibitor enfuvirtide. Proper drug selection for combination therapy is important for maximized effectiveness. Once the right combination has been determined, patients may acquire their treatment in pill-form to be taken once daily (Lehmann et al., 2019).

Concern over increased side effects has raised the question of when to begin ART treatment. Subsequent studies have revealed the importance and added benefits of initiating ART early rather than delaying it. Thus, it is recommended that ART is started within a few weeks after testing positive for HIV. This should be preceded by a resistance test to anticipate viral-induced drug resistance and ensure ART effectiveness. Comorbidities must also be considered in the selection of combination drugs, especially as patients age over time. Additionally, ART requires the consultation of highly experienced experts in cases of pregnancy (Lehmann et al., 2019).

ART combination drugs may require re-evaluation in the case of virological failure, where levels of HIV-RNA are repeatedly measured to be over 200 copies/ml in the blood. However, other factors must also be taken into account, including the patient's adherence to ART, other medications taken simultaneously, drug resistance, or the presence of concomitant diseases (Lehmann et al., 2019).

While a treatment that fully eradicates HIV has not yet been discovered, long-term treatment in the form of ART has been demonstrated as an effective alternative. ART specifically prevents opportunistic infections, premature death, and further transmission of the virus. Additionally, the risk of perinatal transmission is reduced to 1% after treatment is initiated in a pregnant mother (Lehmann et al., 2019).

Novel research indicates the possibility of shifting to a two-drug regimen instead of the traditional three-drug combination in current ART. Scientific evidence gained from multiple studies shows improved levels of tolerability, lower toxicity, and greater viral suppression. Furthermore, the dual drug model reduces risks of cardiovascular disease as well as bone and

renal toxicities. Additionally, this treatment alteration reduces therapy costs and thus expands the availability of treatment to more people. Within the US, an estimate of between 500 million and 3 billion dollars would be saved in ART costs in the span of five years if two antiretroviral drugs rather than three were used to treat HIV patients. Internationally, the cost differential would have even more significance. Already, certain international standards have adopted the dual drug therapy option, whose simplified yet effective regimen includes an integrase inhibitor with elevated levels of inhibitor and reverse transcriptase inhibitor (Duarte and Soares, 2019).

Opioid Crisis in HIV Patients

Additional research has uncovered the major effect opioids such as morphine and heroin have on the immune system, particularly on the enhancement of HIV-1 infection. This research was stimulated by consideration of the overlap between the HIV-1 epidemic and the opioid crisis. Since then, numerous research studies have been performed that demonstrate the immunosuppressant properties of opioids and identify the specific effects of opioids on the enhancement of HIV-1 infection (Eisenstein, 2019).

Opioid Receptors

Three major opioid receptors have been identified: mu opioid receptor (MOR), kappa opioid receptor (KOR), and delta opioid receptor (DOR). Additionally, the ligands which bind to these receptors have been identified as the neuropeptides beta-endorphin (MOR), dynorphin (KOR), and methionine-enkephalin (DOR) (Eisenstein, 2019). These opioid receptors are expressed in the central nervous system (CNS) and on the surfaces of many cells within the immune system (Steele et al., 2003). Morphine and heroin have been shown to have the greatest binding affinity for the MOR, inducing intracellular receptor signaling (Eisenstein, 2019).

Major Opioids Receptor Agonists and Antagonists

Study of the immunological effects of opioids first requires adequate understanding of the opioids themselves. Derived from the opioid poppy plant, morphine is an alkaloid which has a high binding affinity for MOR. The effects of this drug have been studied in human and murine models, both *in vitro* and *in vivo*. A similar though synthetic version of morphine is heroin, which contains diacetyl, but is metabolized to morphine. Major opioid antagonists include naloxone and naltrexone, which bind to all three opioid receptors. A third major opioid antagonist is beta-funaltrexamine (beta-FNA), which binds selectively to MOR. As the commercially-sold version of naloxone, Narcan® has a greater affinity for MOR than morphine, and can mitigate morphine-induced effects upon binding without stimulating receptor signaling (Eisenstein, 2019).

Opioid Enhancement of HIV Infection

Increased CXCR4 and CCR5 expression. One research study demonstrated enhanced CXCR4 and CCR5 expression as a result of opioid exposure. In the study, CD14⁺ monocytes and CD3⁺ lymphoblasts were exposed to DAMGO, which is a highly specific MOR agonist with the ability to simulate the effect of morphine. Testing revealed increased levels of CXCR4 and CCR5 receptors on the cell surfaces. However, this was only observed in activated T cells, while significant change was not detectable in resting cells (Steele et al., 2003). A similar effect of CCR5 upregulation in macrophages and CXCR4 and CCR5 upregulation in astrocytes was observed. This correlation of opioid exposure and CXCR4 and CCR5 upregulation is significant, as these coreceptors are required for HIV-1 binding and fusion with a host cell.(Eisenstein, 2019).

Increased p24 levels. Further testing of HIV-1 cells exposed to DAMGO revealed increased levels of HIV-1 p24 antigen. Similar results were also observed in HIV-1 cells exposed to morphine. This further confirmed the causative link between opioids and the enhancement of HIV-1 infection (Steele et al., 2003).

Downregulation of antiviral miRNA. In addition, morphine and heroin have been shown to negatively impact antiviral innate immunity defenses against HIV-1 infection in macrophages. Within macrophages, restriction microRNAs (miRNAs) are expressed which target parts of the HIV-1 genome and inhibit translation of key HIV-1 proteins, including TAT and REV. Specifically, miRNA-28, miRNA-125b, miRNA-150, miRNA-223, and miRNA-382 perform these inhibitory functions and help impede HIV-1 infection. Significantly, these miRNAs are also often plentiful in resting CD4⁺ T cells and monocytes, and are often expressed in response to IFN-alpha/beta signaling. However, a decrease in miRNA expression was observed in macrophages treated with heroin. Specifically, downregulation of miRNA-28, miRNA-125b, miRNA-150, and miRNA-382 were detected (Wang et al., 2015).

Suppression of IFN-alpha/beta and suppression of cytokine production. Additionally, heroin was shown to suppress IFN-alpha and IFN-beta expression in macrophages. Heroin-induced suppression of IFN-alpha/beta may be a causative link to reduced levels of miRNA expression, as IFN-alpha/beta stimulates miRNA expression (Wang et al., 2015). Furthermore, in HIV-infected cells treated with heroin, the downregulation of cytokine production was observed. Specifically, significantly reduced levels of IL-1 β , IL-6, IFN- γ , and TNF- α were detected (Meijerink et al., 2015).

Opioid Management

The need for improved management of treatment with opioids has gained awareness in recent years. Within the HIV- infected population, chronic pain is more commonly experienced and treated with opioids. However, long-term prescription of opioids for chronic pain may increase the risk of opioid abuse disorder. In addition, those infected with HIV are often more likely to have substance use disorders and mental illness, which further increases opioid abuse risks. This situation demands increasing awareness, attention, and action (Cunningham, 2018).

Chronic opioid therapy has been identified as a main cause of the opioid crisis (Carroll et al., 2019). Data from the Centers for Disease Control and Prevention (CDC) reveal that over 70,000 people died in 2017 due to drug overdoses. Significantly, approximately 68% of these deaths were linked to opioids obtained illicitly or via prescription (CDC, 2019). Further research is needed regarding how many of these overdoses were linked to HIV patients receiving opioid treatment for chronic pain. Nevertheless, in seeking to lower such devastating statistics, opioid management must improve. However, this is undeniably complex, and involves the role and responsibility of the HIV-infected individual as well as the HIV clinician and healthcare system.

In a recent study, multiple physicians were interviewed regarding their experience in and knowledge of chronic pain management in HIV-infected individuals. This study revealed that clinicians felt a lack of confidence and knowledge about safe opioid prescription management. Clinicians stated they had little previous experience regarding this. Furthermore, clinicians were concerned about straining clinician-patient relationships in their attempts to better monitor opioid usage and results. Clinicians emphasized the importance of having a trusting relationship with the patient to ensure successful HIV monitoring. Additionally, clinicians feared that patient

retention would be negatively affected. Finally, clinicians voiced concern over increased volume of administrative tasks if opioid monitoring protocol were to increase (Carroll et al., 2019).

The study offered solutions, many of which were enthusiastically received by the concerned clinicians (See Table 2). This included offering more academic sessions which better informed clinicians on how to properly and safely manage opioid prescriptions. An increase in support staff was also suggested and well received. Finally, the solution to train and hire more addiction specialists was also approved by clinicians (Carroll et al., 2019).

Initiating Treatment with Opioids	Determining Opioid Selection, Dose, Duration, Follow-up, and Discontinuation	Assessing Risks and Harms of Treatment with Opioids
Nonpharmacologic and nonopioid therapies are preferred Establish treatment goals (pain and function levels) Discuss risks and benefits of opioid use and patient and practitioner responsibilities	Prescribe immediate-release (not long-acting) formulations Prescribe lowest effective opioid dose (<50–90 morphine milligram equivalent) Prescribe no greater quantity than needed (enough for ≤3–7 days) Reevaluate effectiveness. If risk or harms are substantial, taper or discontinue	Evaluate and mitigate harms Consider naloxone Use a prescription drug monitoring program Order urine toxicology tests Avoid concurrent use of opioids and benzodiazepines Offer buprenorphine or methadone to treat opioid use disorder

Table 2. CDC Guidelines for Centers Prescribing Opioids for Non-Cancer-Related Chronic Pain.

The CDC guidelines provide a framework to reform approaches to prescribing and treating with opioids. Data obtained from (Cunningham, 2018).

Conclusion

In conclusion, human immunodeficiency virus, also known as HIV, is a devastating disease which has affected and still affects millions globally. While many cases of HIV exist in the United States, HIV is most prevalent in sub-Saharan Africa (Williams et al., 2017). While HIV may be identified as type 1 or type 2, type 1 has been diagnosed globally, while type 2 is restricted to specific areas of the globe (Vidya Vijayan et al., 2017). Numerous studies have been

conducted that detail the viral genome and reveal the molecular mechanisms by which the virus enters and infects host cells. HIV is a retrovirus which encodes its genome in the form of RNA. Infection occurs primarily in CD4⁺ T cells, which normally possess coreceptors CCR4 or CXCR5. Once in the host cell, the viral genome is replicated and integrated into the host cell genome. In activated CD4⁺ T cells, the entry and attack of HIV leads to a drastic host cell response, often resulting in apoptosis. However, in resting CD4⁺ T cells, the viral genome may remain integrated and intact in the host cell for a later attack (Doitsh and Greene, 2016).

A significant reduction of CD4⁺ T cells often occurs before an individual is aware of infection. Within 2-4 weeks of infection, individuals may experience flu-like symptoms. As the disease develops, symptoms increase in severity (Owen et al., 2013). The progression of HIV often involves the development of disease complications, including different varieties of HIV-associated psoriasis and sensory neuropathy (Ceccarelli et al., 2019; Melli et al., 2006).

Currently, the most effective treatment option exists in the form of ART, which involves the strategically chosen combination of three drugs that function to inhibit HIV-encoded proteins. Most commonly, two nucleoside reverse-transcriptase inhibitor are used in conjunction with an integrase inhibitor. While ART fails to eradicate the virus, it has demonstrated high levels of efficacy in combatting the virus (Lehmann et al., 2019).

In addition to ART, opioids are commonly prescribed to people living with HIV to combat chronic pain experienced on a daily basis. However, extensive research studies have demonstrated the immunosuppressant properties of opioids such as heroin and morphine.

Significantly, the intersection of the HIV epidemic and opioid crisis requires the attention of

researchers and clinicians. Additionally, clinicians, especially those who prescribe medication, must be adequately informed and properly equipped to address these complicated factors.

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