An update on current HIV treatments

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Abstract. The roll-out of antiretroviral therapies (ART) has greatly assisted in reducing the morbidity and mortality rates caused by HIV. However, ART is incapable of eliminating the latent Human Immunodeficiency Virus (HIV), leading to life-long treatment being undertaken. Current HIV cures can be classified into the sterilizing cure, where the HIV latent reservoir is fully eliminated, or the functional cure, where prolonged suppression of latent HIV is achieved. Broadly Neutralizing Antibody (bNAb) is a type of sterilizing cure which targets an epitope on HIV Envelope (Env) protein. Studies indicated that a combined bNAb regiment is better than bNAb monotherapy due to the ability to avoid HIV escape variants. Another type of sterilizing cure is known as “shock and kill” strategy, comprising a latency-reversing agent which activates latent HIV and eliminates it with a “kill” agent. Alternatively, functional cure such as the “Block and lock” strategy utilizes a latency-promoting agent to “block” viral transcription and prevent it from being activated for a prolonged period. Further research and clinical tests are required to develop an HIV cure.

Keywords: Human Immunodeficiency Virus (HIV), HIV life cycle, HIV antiretroviral therapies (ART), HIV treatments, Broadly Neutralizing Antibodies (bNAb).

1. Introduction

The Human Immunodeficiency Virus (HIV) is a positive-stranded RNA virus belonging to the Retroviridae family. HIV is further distinguished by their subtypes: HIV-1 and HIV-2. The subtype responsible for the infections in humans is HIV-1 [1].

HIV is known for its capability to cause Acquired Immune Deficiency Syndrome (AIDS), a disease known to burden 39 million people worldwide in 2022, accounting for 40 million deaths ever since the beginning of the epidemic [2]. HIV is prevalent amongst low- and middle-income countries in Southern and Eastern Africa, where infected adults account for 80% of the total HIV-infected persons globally [2].

HIV is primarily transmitted through body fluids such as blood. The primary target for HIV is CD4-expressing T cells. After initial infection, HIV will infect regional lymph nodes, such as the draining lymph nodes, and begin its initial replication, this stage is typically called primary infection. Around two weeks after primary infection, secondary infection occurs as the virus disseminates into the bloodstream, infecting other susceptible cells amongst lymphoid and non-lymphoid tissues. Notably, the virus can establish a latent reservoir within memory T cells, where HIV DNA is integrated into the host chromatin [1].

Given the prevalence of this disease, significant amounts of attention were placed on it, leading to an exponential increase in understanding its life cycle, along with significant developments in HIV treatments. The development of antiretroviral therapies (ART) marks a milestone in our combat against HIV [1]. Currently, ART is the most efficient drug to be used against HIV, and life-long ART treatment has been recommended by the World Health Organization (WHO) for HIV diseases [1].

Despite the successes of ART treatment in suppressing HIV replication, it cannot eliminate the latent reservoir. This typically results in viral rebound after ART is stopped, rendering life-long ART treatment necessary [3]. Given the situation, there is a dire need for an alternative treatment that can eliminate HIV latent reservoirs, leading to viral suppression without continuous treatment.

This review will introduce HIV life cycle and pathogenesis. Along with this, insights on current HIV treatments will also be presented.

2. Background on HIV and Current Treatments

2.1. Brief overview of the HIV replication cycle

The replication cycle of HIV can be briefly broken down into the early phase and the late phase. The early phase involves receptor binding, viral membrane fusion, reverse transcription and DNA integration. The late phase refers to the processes from integrated HIV gene expression to releasing new HIV virions [4].

Viral entry begins with the binding of viral Env glycoprotein (gp120 and gp41) to primary CD4 receptors. Upon binding, the gp120 glycoprotein will undergo structural changes, exposing domains capable of binding to 7-transmembrane, G-protein coupled co-receptors known as chemokine receptors (CCR5 and CXCR4). HIV binding to CCR5 receptors is known as M-tropic virus, and this typically occurs during acute early infection. On the other hand, HIV can bind to the CXCR4 chemokine receptor, and this binding typically occurs during chronic infection. The virus will initiate membrane fusion after binding to the chemokine receptor, where the viral membrane and the cell envelope will be brought together. HIV gp41 protein was found to interact with the two membranes and promote membrane fusion (Figure 1) [4].

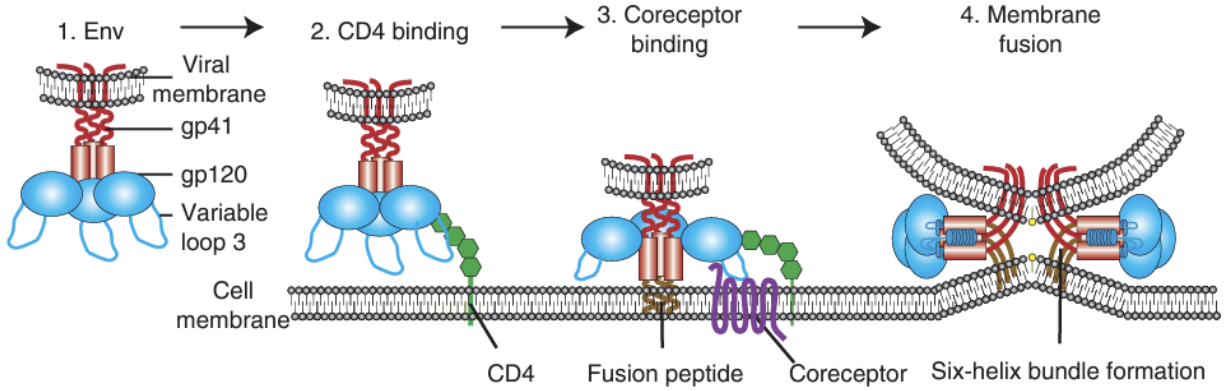

Figure 1. HIV receptor binding. Viral binding and entry are initiated by the binding of HIV Env glycoproteins (gp120 and gp41) to the corresponding CD4 receptor. Structural changes after binding to the primary receptor will cause the virus to further bind to a co-receptor known as chemokine receptor (CCR5 and CXCR4). Next, fusion peptide is exposed and will mediate the membrane fusion event between the virus and the host cell membrane. Figure adapted from [4].

After the membrane fusion event, the virus will release its genome into the cytoplasm, where the early phase of viral replication takes place. Within the cytoplasm, the virus will utilize an enzyme known as reverse transcriptase to assist with generating a double-helix DNA. The reverse transcriptase will initially perform minus-strand polymerization by treating the positive-stranded HIV RNA as the template and a host tRNA as a primer. Reverse transcriptase also contains a ribonuclease H domain that degrades the RNA template strand. Notably, the reverse transcriptase is very error-prone. Therefore, it tends to alter the pathogenicity of the virus. Ultimately, a double-helix HIV DNA will form and will be further processed [1].

The double-helix HIV DNA will then integrate, through nuclear pores, into the cell nucleus. Then, the virus DNA will integrate into the host DNA. This process is catalyzed by the viral integrase protein, which cleaves nucleotides of each 3' end of the double helix viral DNA, generating two sticky ends that enable integration into the host chromosome [1].

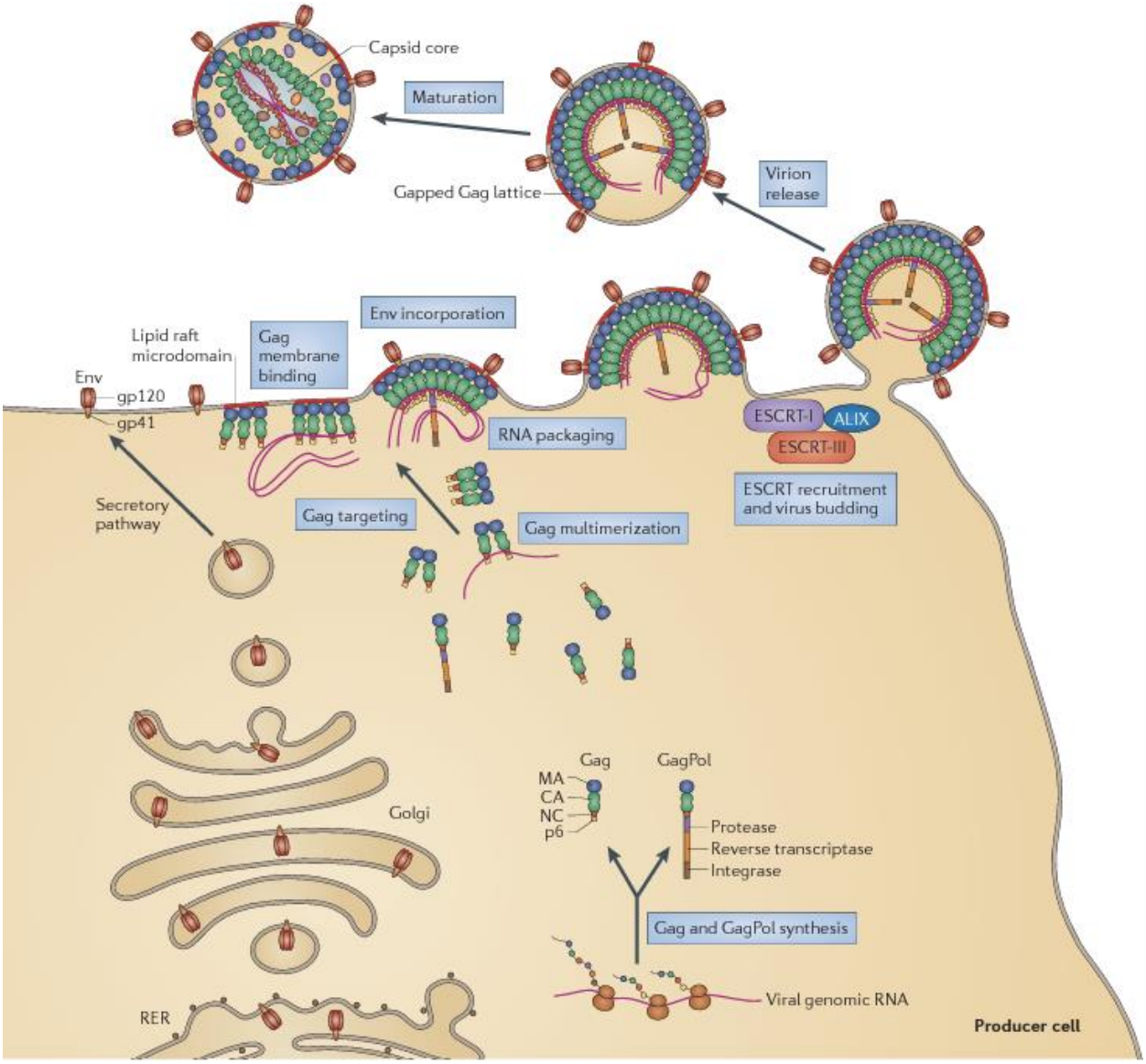

Figure 2. Late phase HIV life cycle. Upon the transcription of the integrated HIV gene, the viral RNA will be exported to the cytoplasm for further translation. The Env glycoprotein crucial in viral attachment, first traffics from the rough endoplasmic reticulum (RER), then to the Golgi and finally to the plasma membrane. The Gag and the GagPol protein will be translated from viral RNA, then will assemble with the rest of the viral proteins to form an immature Gag lattice. Finally, maturation of the viral particle catalyzed by the cleavage of Gag and GagPol by the viral protease. Figure adapted from [5].

In the late phase replication cycle, host polymerase will transcribe the integrated HIV gene, producing viral RNA, which will be exported to the cytoplasm. Translation of these RNA will produce viral proteins: accessory and regulatory protein, Gag precursor protein, GagPol precursor protein and the envelope (Env) glycoprotein. Gag has several functions but is key in recruiting viral genomic RNA, incorporating the Env protein and mediating capsid core assembly. GagPol protein contains essential viral enzymes, viral RT, viral integrase and viral protease. The protease will facilitate viral maturation by cleaving the Gag precursor. Finally, Env glycoprotein comprises gp120 and gp41, which are crucial in viral receptor recognition. The viral particle assembly process begins at the plasma membrane, where the Gag protein, GagPol precursor, the viral RNA, and the Env glycoprotein form an immature Gag lattice. The lattice will then recruit several proteins of the endosomal sorting complex required for transport (ESCRT) machinery, leading to it budding away

from the plasma membrane. Finally, the viral protease from the GagPol precursor protein will cleave Gag and GagPol, leading to the maturation of the viral particle (Figure 2) [5].

2.2. Current ART treatment

As a first-line HIV treatment recommended by WHO, the ART treatment greatly reduced the morbidity and mortality caused by HIV [1].

Current antiretroviral drugs can fall into seven major categories, classified by their targets in the HIV life cycle: (1) Inhibitor of viral protease, (2) Integrase strand transfer inhibitor, (3) non-nucleoside reverse transcriptase inhibitor, (4) nucleoside reverse transcriptase inhibitor (5) Fusion inhibitor (6) Antagonist of CCR5 receptor (7) CD4 entry inhibitors [1].

Amongst these categories of ART, a combination of an integrase strand transfer inhibitor with two nucleoside reverse transcriptase inhibitors was previously suggested to be an initial therapy against HIV [1].

Tenofovir is the most used nucleoside reverse transcriptase inhibitor. The Food and Drug Administration (FDA) approved the use of Tenofovir disoproxil fumarate (TDF) in 2001 to combat HIV. In a randomized controlled trial carried out by DeJesus and colleagues, 89% of patients on TDF treatment were found to have HIV suppression at the 96-week of treatment [6].

In recent years, a prodrug of Tenofovir, Tenofovir alafenamide (TAF), was selected over TDF due to its ability to have less severe adverse effects than TDF. Notably, one study suggested that across 96 weeks of drug regimen, patients receiving TAF experienced no signs of renal tubulopathy, while ten patients on TDF experienced renal tubulopathy [7].

Common integrase strand inhibitors provided are dolutegravir (approved by the FDA in 2013) and bictegravir (approved by the FDA in 2018). HIV suppression was measured during week 48, and results indicated that vial suppression was achieved in 92.4% of the population taking bictegravir and 93% of the population taking dolutegravir. Notably, incidents of nausea were less in patients taking bictegravir than in patients taking dolutegravir (bictegravir: 10% and dolutegravir: 23%) [8].

2.3. Issues with current ART treatment

Despite the success of ART treatment, many issues persist. One major issue is that ART treatment comes with adverse effects and toxicities. TDF drug regimen was also known to cause various adverse effects. Notably, TDF is known to be nephrotoxic and was found to cause renal failure. A previous study indicated that, from week 24 to 144, patients with long-term exposure to TDF experienced a 30% increase in renal-associated disease prevalence. In comparison, patients with no exposure to TDF only experienced a 6% increase in renal-associated disease [9]. In line with this, a study stated that 10 out of 2962 patients on TDF treatment experienced renal tubulopathy, while 14 out of 2962 patients had to withdraw from the trials due to renal-related diseases through 96 weeks of treatment [7].

Another issue is virologic failure, where patients on ART experience viral load rebound, measured through HIV RNA. One of the major causes of virologic failure happens to be the development of drug-resistant HIV mutations. One European study, with 260 patients initiating non-nucleoside reverse transcriptase inhibitor, indicated that the detection of drug-resistant mutation on HIV was correlated with an increased chance of virologic failure [10].

Interestingly, resistance mutations are thought to develop due to sub-optimal ART intake. In support of this, a study involving 1926 patients indicated that around 78% of patients develop drug-resistance mutations for non-nucleoside reverse transcriptase inhibitors after first-line non-nucleoside reverse transcriptase inhibitor ART treatment [11].

ART treatment was suggested to be implemented during acute HIV infection. A cohort study indicated that ART regimens given to patients during acute HIV infection can reduce the rate of CD4 cell decline after ART discontinuation [12]. Despite the evidence showing that an ART regimen provided during acute HIV infections poses benefits, the ART regimen cannot prevent viral latency establishment even if provided during the acute phase. Henrich and colleagues reported that despite

providing the patient with an ART regiment during early acute HIV infection, viral rebound was observed seven months after one patient stopped ART, and the latent reservoir, measured by mathematical models, persists [13]. This is a major downside for ART therapy, as life-long treatment is typically required even when treatment is initiated during the acute phase of infection.

3. Prospective Hiv Cures

Given the limitations of ART treatment, many alternative approaches were sought to treat HIV. Current HIV cures can be classified as a sterilizing and a functional HIV cure. A sterilizing cure is typically defined as the suppression of viral viraemia through the complete abolishment of replication-competent virus (the latent reservoir). A functional cure is represented as the prolonged suppression of HIV without treatment [3].

3.1. Sterilizing HIV cure – Broadly Neutralizing Antibodies (bNAb)

As an approach for achieving sterilizing HIV cure, therapeutic vaccines which utilizes broadly neutralizing antibodies (bNAb) were sought due to their ability to enhance innate immunity or to elicit HIV-specific cytotoxic T-lymphocytes. These mechanisms will ultimately lead to the destruction of latent HIV reservoirs. bNAb are antibodies that can generate protection against most circulating strains of HIV [3].

Briefly, two major components comprise the bNAb: the antigen-binding fragments and the crystallizable fragments. The antigen-binding fragments recognize a specific antigen of HIV, typically the Env protein. The HIV Env protein harbours several conserved domains which are targeted by bNAb (Figure 3). These domains are also known to play an important role in viral entry. Therefore, it was also suggested that bNAb binding to these domains could potentially elicit a neutralizing effect, preventing virus infection [3]. On the other hand, the crystallizable fragments function by interacting with other components of the immune system and initiating the host immune response to eradicate the viral particle [3].

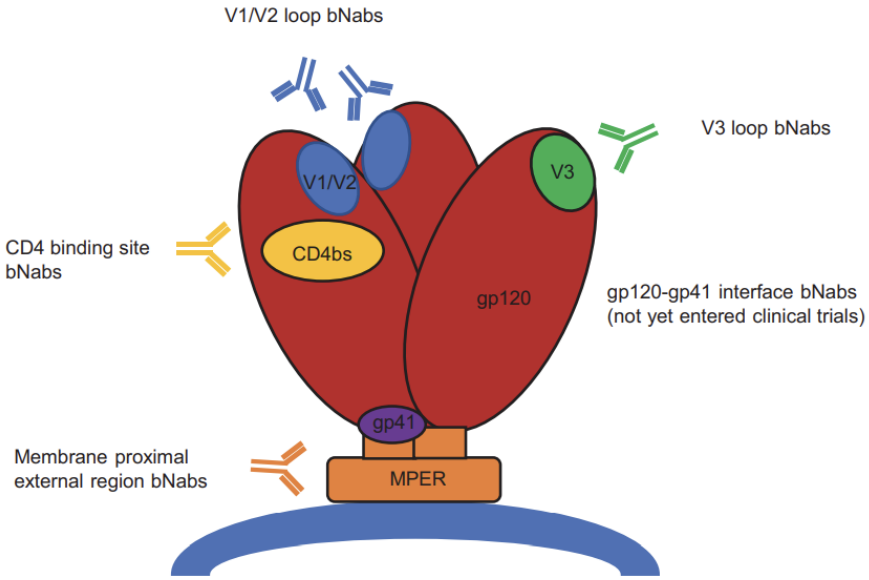

Figure 3. Illustration of common epitopes for bNAb against the HIV Env protein. Figure adapted from [3].

Clinical studies on bNAb have shown HIV suppression amongst patients chronically infected with HIV. A phase 2 clinical trial on bNAb 3BNC117 targeting the Env protein of HIV, involving 13 participants, indicated that the virus was suppressed for 19 weeks compared to control, which experienced rebound between weeks 2-3. The same study also noted that viral resistance was present after the viral rebound when antibody levels were reduced below 20 μg ml^ (-1) [14]. This indicated that escape variants, which developed resistance to the bNAb, were present during the study. To avoid

escape variants from developing, the combined usage of bNAb was sought. A phase one trial tested the effect of bNAb 3BNC117 and 10-1074 on seven patients. The report stated that viral suppression lasted for as long as three months, and no antibody resistance was developed [15]. This finding indicated that combined bNAb therapy works better than bNAb monotherapy, highlighting the potency of this type of vaccine in combatting latent HIV.

3.2. Sterilizing HIV cure – "Shock and kill" strategy

The "shock and kill" strategy, unlike bNAb, aims to activate latent cells and then target the latent cells using anti-retroviral drugs or by modulating the immune system. The system comprises a latency-reversing agent (or "shock" agent) that aims to activate latent HIV and a "kill" agent that functions by mediating the death of reactivated latent cells [3].

The most widely studied latency-reversing agent is known as histone deacetylase inhibitors. Vorinostat is a histone deacetylase inhibitor and was previously shown to effectively decrease RNA expression by 4.8-fold, after analyzing T cells cells retrieved from eight patients undergoing ART treatment [16]. Despite the effectiveness of histone deacetylase inhibitors in activating latently infected cells, they were incapable of reducing these cells, as suggested by clinical trial results carried out on histone deacetylase inhibitor Panobinostat [17].

"Kill" agents are used to eliminate reactivated latent cells. One approach currently being investigated is to induce HIV-specific apoptosis through proteasome inhibitors. HIV can resist apoptosis by cleaving the host procaspase-8 protein with a protease enzyme. The product, Casp8p41, is known to activate Bak protein and lead to apoptosis or to form a complex with Bcl2 and initiate a cascade of events that prevents cell death [18]. Notably, a past study indicated that one proteasome inhibitor known as ixazomib prevents the degradation of Casp8p41, effectively increasing the levels of Casp8p41 and enhancing the chance of Casp8p41-dependent apoptosis [18]. In addition, a study involving 16 ART-suppressed patients over the course of 24 weeks indicated that ixazomib was capable of reducing HIV reservoir size after utilizing intact proviral DNA assay [19].

3.3. Functional HIV cure – "Block and lock" strategy

Alternative to the "Shock and kill strategy", the "Block and lock" strategy does not aim to eliminate the latent reservoir but to prolong the latent state of the virus so that the active life cycle is inhibited. This treatment is dependent on a latency-promoting agent, which can "block" viral transcription, ultimately driving the virus to prolonged latency via the "lock" phase [20].

Transcription of the integrated HIV involved the Tat protein, and low levels of Tat protein were characteristic of HIV latency. Didehydrocortistatin A (dCA) is a latency-promoting agent which can directly bind the Tat protein, preventing HIV transcription. Mousseau and colleagues discovered that dCA could mediate viral transcription suppression upon antigenic stimulation [21]. In accordance with this result, the combination of ART with dCA was found to suppress HIV-1, with lower viral RNA detected from samples treated with both ART and dCA compared to samples treated with only ART. In the same study, researchers also reported that after treatment was ceased, viral rebound was lower in mice treated with both ART and dCA, compared to samples treated with only ART until day 26, where mean viral loads were not significantly different [20]. These findings highlight the potency of the "Block and lock" strategy against latent HIV.

4. Conclusion

Despite the success of ART in combatting HIV, many issues persist. Notably, the persistence of latent HIV reservoir means that life-long treatment is typically required. Lack of adherence to treatment and ART toxicity highlights the need for an alternative treatment to eliminate the HIV reservoir.

Current interventional strategies against HIV can be broadly classified into a functional and a sterilizing cure. The sterilizing cure requires the removal of all replication-competent virus, while a functional cure only requires the prolonged suppression of HIV.

Approaches to achieving a sterilizing cure include bNAb vaccines, where bNAb can both bind to an epitope of HIV Env protein and also initiate a host immune response to clear latently infected cells. Further studies indicated that a combination of bNAb functions better than bNAb monotherapy. Alternatively, a latency reversal agent is initially used in the "shock and kill" strategy to activate latent HIV, then, a "kill" agent is used to eliminate the activated cells. Vorinostat is a histone deacetylase inhibitor that functions as a latency reversal agent, and ixazomib is a proteasome inhibitor acting as a "kill" agent.

Functional cure can be achieved using a "Block and lock" strategy, where a latency-promoting agent that prevents HIV gene expression is utilized. Didehydrocortistatin A (dCA) is a very promising latency-promoting agent under investigation.

Long-term research and commitment to these potential HIV cures is necessary to exploit their therapeutic potential, leading to an HIV cure.

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