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GRADUATE REVIEWS

The Possibilities of Finding a Cure for HIV: A Literature Review

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ABSTRACT

The human immunodeficiency virus (HIV) is a major worldwide health concern, affecting millions of people globally, and when untreated progresses into acquired immune deficiency syndrome (AIDS). With the availability of antiretroviral therapy (ART), HIV infection is defined as a manageable, but not curable, chronic health condition. ART inhibits viral replication and prevents HIV transmission but does not eliminate the virus due to viral latency in memory T cells, exacerbated by the rise in drug resistant mutations (DRMs), so lifelong treatment and monitoring is required. In this review, we discuss the justifications and research approaches towards finding a "cure" for HIV i.e. complete elimination or control of the virus without the need for further treatment. The two main barriers to developing a cure for HIV infection are the property of HIV viral latency and high mutation rate of the virus. A few cases of HIV have been cured through bone marrow transplants to treat acute myeloid leukaemia, where the donors had rare mutations in the CCR5 gene, required for viral entry. More viable approaches to a cure include the "Shock and Kill" method which aims to use reverse viral latency allowing these cells to be detected and destroyed with ART, and the "Block and Lock" method aims to block viral transcription in HIV-infected latent cells, preventing a rebound viral replication after the cessation of ART. The possibility of vaccination has been widely explored, but an effective HIV vaccine has yet to be developed after more than 40 years of the pandemic. Currently, the "Block and Lock" approaches appear to be the most favourable, possibly in conjunction with other recently developed interventions such as passive immunisation with broadly neutralizing antibodies. However, approaches taken to develop a cure for HIV cannot be detached from ethical concerns which need to be acknowledged and navigated.

Keywords: Human immunodeficiency virus, viral latency, HIV treatment

1 Introduction

The human immunodeficiency virus (HIV) remains a major worldwide health concern, with roughly 40 million people living with the virus in late 2023, two thirds of whom live in the WHO African Region, which has the biggest burden of the disease [1]. Globally, HIV infection is estimated to have claimed 42.3 million lives since the virus was first detected in the 1980s, with active transmission persisting, and in many cases rising, in all countries worldwide [1]. HIV infection is defined by the World Health Organisation as a manageable, but not curable, chronic health condition. However, this depends on firstly access to effective HIV testing and treatment, and secondly the continuing effectiveness of current anti-retroviral medication. In 2023 alone, despite the plethora of anti-retroviral treatments and testing methods now available, it is estimated there were 1.3 million new HIV infections and 630 thousand HIV related deaths globally [1]. Furthermore, young people (15-24 year olds) are considered to be at particularly high risk from HIV infection, due to lack of awareness concerning appropriate preventable measures or limited access to services, and account for nearly 30% of new HIV infections annually [2].

HIV came to the fore when the "AIDS (acquired immune deficiency) crisis" began in the early 1980s. The HIV virus, the causative agent of AIDS, was first discovered by Luc Montagnier and Françoise Barré-Sinoussi in 1983 and was originally named Lymphadenopathy-Associated Virus (LAV) before being renamed to HIV in 1986 [3]. HIV is part of the retroviridae family with a lipid envelope to protect the capsid containing two positive-sense single stranded RNA molecules and key enzymes crucial for viral replication [4] (Figure 1). In 2006, the origin of HIV was identified as the Simian Immunodeficiency Virus (SIV) in chimpanzees, and it is likely the virus crossed over to humans as early as the late 1800s to a population of hunter-gathers in the Cameroon via open wounds during hunting activities, and subsequently slowly migrated through the human population [5]. The earliest detectable confirmed case of HIV was identified through retrospective screening of a blood sample taken in 1959 from a male in the Democratic Republic of Congo, where the virus was understood to have been expanding since the 1920s following major industrial and transport developments in the area [3, 6].

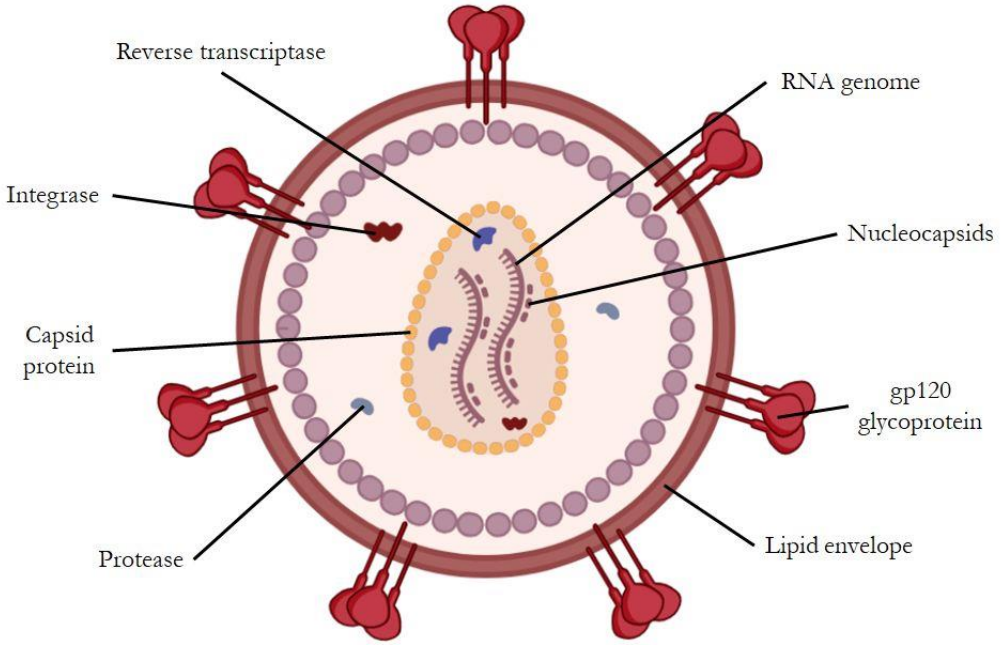

Figure 1: *The structure of the HIV virion. The basic structure of the HIV virion is shown to illustrate the genomic material (two positive-sense single strands of RNA) surrounded by the nucleocapsid, and the three key viral enzymes: Reverse transcriptase, which transcribes the viral RNA into pro-viral DNA; Integrase, which inserts the pro-viral DNA into the host chromosome; and HIV protease, which plays a key role in viral maturation, and the gp120 glycoprotein, which enables attachment and entry into the host cell. Adapted from Levintov and Vashisth [4]. Image created using BioRender.com [7].*

HIV can be transmitted through a range of bodily fluids containing the virus or infected cells, most commonly through sex or sharing needles, and can also be transmitted congenitally [8]. Upon infection, the virus targets the CD4 receptor of T helper cells, monocytes and macrophages via the viral gp120 glycoprotein (envelope protein). The HIV gp120 then undergoes a conformational change enabling binding to a co-receptor, CCR5 or CXCR4, which then triggers further confirmational changes enabling fusion between the viral and host cell membrane, allowing entry into the host cell [9]. The initial symptoms of HIV, if any, can appear similar to the common flu, apparently self-resolving after a few weeks. The lack of distinctive symptoms means that HIV can only be diagnosed through tests that specifically detect the HIV virus or antibody. Tests can also show false negatives if conducted too early after exposure, as virus or antibody levels have to reach a certain concentration to be detected [8].

Over time, an untreated acute infection develops into a chronic asymptomatic infection which gradually weakens the immune system, leaving the infected person vulnerable to a broad range of opportunistic infections and cancers. As such, many cases can be undetected for years, during which time active transmission can occur. If still untreated, the HIV infection eventually develops into AIDS. AIDS is the final and most severe stage of HIV infection, characterised by drastically damaged immune systems, and can cause death within three years if left untreated [8]. Fortunately, the risk of HIV transmission is greatly reduced with the use of condoms and frequent testing, and is currently fully treatable provided the patient can access effective anti-retroviral medication for lifelong treatment [1].

In this review, we discuss the different research approaches for finding a cure to HIV. For the purpose of this review, a cure is defined as a treatment that either removes HIV from the body entirely, permanently prevents latent T cells from reactivating and producing the virus without ART, or actively prevents infection using the body's own immune defence mechanisms [10].

2 HIV Treatment and Barriers to Developing a Cure

The current treatment for HIV is antiretroviral therapy (ART) which was first developed in 1987. Azidothymidine, a nucleoside reverse transcriptase inhibitor (NRTI), hindered viral replication and disease progression by acting as a competitive inhibitor to HIV, but had a range of side effects and HIV strains rapidly developed [11]. Since then, many more antiretroviral drugs have been developed and other mechanisms of inhibition have been discovered. Apart from NRTIs, other common ART drug classes are non-nucleoside reverse transcriptase inhibitors (NNRTI) which bind to HIV reverse transcriptase, integrase strand transfer inhibitors (INSTI) which block the integrase enzyme used to insert HIV DNA into $CD4^+$ cells, and protease inhibitors (PI) which inhibit the HIV protease from correctly processing the viral proteins required for HIV maturation [12]. To reduce the possibilities of developing drug resistance, ART has evolved into a combination of three or more antiretroviral drugs with different targets, so the replication of a virus resistant to one drug would be prevented by the other drugs [13]. Regardless of the drugs involved, successfully blocking viral replication prevents HIV transmission to others, but does not eliminate the virus.

HIV can infect a range of immune cell types, but the most crucial are $CD4^+$ helper T-cells which are central to a functioning immune system. Altered activity and destruction of helper T-cells inhibits their crucial functions, such as the stimulation of innate immune cellular responses and differentiation of $CD8^+$ T cells and B cells [14]. This weakens the immune system, enabling the virus to avoid detection and infect more cells. After HIV infection, $CD4^+$ T cell levels are gradually depleted. As the virus replicates, the cytoplasmic compartments of some T cells begin to swell and lead to cell necrosis, which exposes more cells to the virus [15]. In some cases, an abortive infection can occur where the cell will induce its own death to prevent viral replication within it. HIV is also able to induce apoptosis in non-infected T cells by secreting a range of viral proteins, further depleting healthy $CD4^+$ T cell levels [16].

The two main barriers to developing a cure for HIV infection are the property of viral latency and high mutation rate of the virus. The establishment of viral latency soon after initial infection is a key contributing factor to persistence of HIV in an infected individual [17]. Normally, activated T cells are able to transition

to a memory state after a target antigen has been cleared from the body, enabling a faster immune response in future infections. If a T cell is infected with HIV prior to the transition, a latent HIV infection can be established [18]. These latent memory cells become widely distributed in tissues throughout the body and express little or no viral RNA, so cannot be targeted by ART or the immune system [19]. HIV-infected T cells retain their ability to circulate around the body and potentially infect other cells through cell-cell interactions in the lymphoid organs. The latent memory cells are also able to undergo homeostatic proliferation and establish a latent reservoir within the lymph nodes [20]. Even after years of ART, these latent cells remain in the body and are able to reactivate as soon as treatment is stopped [21]. The role of viral latency in maintaining HIV infection despite treatment with ART is summarised in Figure 2.

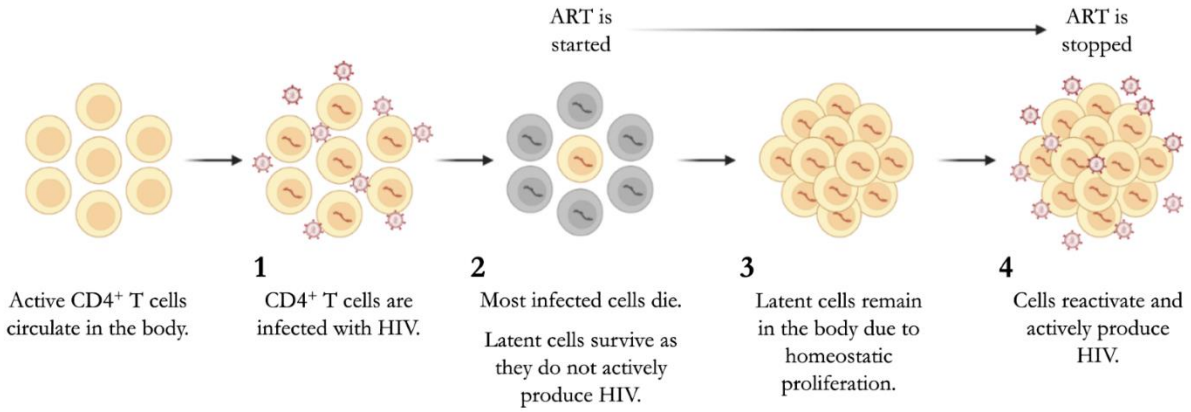

Figure 2: *The role of viral latency in maintaining HIV infection despite treatment with ART. The steps in HIV infection in a patient undergoing ART treatment are shown as follows: 1. HIV infects CD4+ T cells and can replicate. 2. ART kills most of the infected cells, but some cells revert to a latent state and survive undetected as they do not produce active HIV virus. 3. These latent cells remain in the body, widely distributed through tissues, due to homeostatic proliferation. 4. Upon stopping ART, latent cells reactivate and produce new HIV virions. Adapted from Ruelas and Greene [22]. Image created using BioRender.com [7].*

The potential reactivation of latent reservoirs requires HIV patients to receive ART treatment for life, which can be an economic burden for individual patients or government healthcare providers [10]. Ideally, blanket testing could be used to detect all HIV cases and subsequent ART treatment would eliminate any possibility of transmission, effectively eradicating the virus in the next generation. However, even within the currently detected cases, only 60% of people are receiving ART [10]. ART can also be given as a preventative measure ("pre-exposure prophylaxis"), but as with any drug, ART can have side effects and can contribute to unwanted drug interactions, with rising drug resistance a common and re-occurring problem [23].

Another barrier to developing a cure for HIV is the virus' ability to mutate. Of all the known retroviruses, HIV has the most genetic diversity due to its high mutation rate. While not every mutation may have a positive effect on the virus' survival, some mutations show signs of drug resistance or evade the immune system in an unexpected way. When ART is administered, these mutations may survive and continue to replicate until the drug-resistant strain becomes the dominant strain in the body [24]. Drug resistant mutations (DRM) may also increase the risk of transmission, as the patient may be unaware of the treatment failure. Although there is usually a follow-up appointment 3-6 months after ART is first prescribed, late detection of ART failure could put the patient and others at risk [25]. HIV has developed several mutations to resist each of the main drug classes used in ART. The most common mutations, *M184V* and *K103N*, give rise to NRTI and NNRTI resistance respectively [26]. NRTI-resistant mutations alter the reverse transcriptase within the HIV virion which changes the structure of the active site and reduce the affinity of the NRTI, as in *M184V,* or enable it to remove NRTI nucleosides that are blocking its function. Similarly, NNRTI-resistant mutations, like *K103N*, change the structure of reverse transcriptase and inhibit the non-competitive binding of NNRTIs. INSTI- and PI-resistant mutations are less common, but have similar

mechanisms where they alter the enzyme structure and reduce the binding affinity of INSTIs to integrase and PIs to protease. Fortunately, HIV has yet to achieve blanket resistance against all types of ART and in some cases like *M184V*, have increased sensitivity to other drugs in exchange [27]. However, it is still a race against time to develop novel therapies before mutations render ongoing ART treatments ineffective in some global regions, which would have a major impact on the incidence and burden of the disease [28].

DRM prevalence has increased exponentially in recent years. A factor that contributes to the development of DRMs is poor treatment adherence [29]. Multiple studies which have attempted to quantify adherence rates with wide-ranging results, but many of these studies find ART adherence to be below the UNAIDS targets of 95% adherence by 2025 [1]. For example, a systematic review and meta-analysis the prevalence of adherence to ART in orphaned children and adolescents living with HIV/AIDS found adherence rates were highly variable (50.7%-95%) with a pooled adherence across six studies with total ~1000 individuals of 78% [30]. Other studies in different populations have shown adherence rates varied widely depending on the demographics of the study group e.g. 67% among HIV-positive adolescents and young adults in Tanzania [31], 93% among people living with HIV receiving healthcare in Ghana [32] and 16% among people living with mental health disorders attending care facilities in Brazil [33] (cross-sectional studies involving healthcare records and self/physician reporting). A recent cross-sectional study on physician-reported adherence to ART by people living with HIV in the United States (61 physicians reported on 578 patients) found that only 32.7% of patients were fully adherent to their HIV medication [34].

Multiple factors have been identified as impacting adherence rates include level of caregiver or peer support, food insecurity, presence of side effects, mental health status and pill burden [30-34]. ART is a relatively complex treatment regime involving multiple drugs taken on a daily basis with many HIV patients taking 1-4 pills a day [35]. The complexity of a treatment has a direct correlation with treatment adherence [36]. An approach to addressing this is to combine multiple drugs into a single pill which is recommended in countries with developed healthcare systems [35], and there have also been efforts to develop a monotherapy which would have a lower financial burden. A study by Jörimann *et al.* [37] found that an INSTI monotherapy treatment clinically known as dolutegravir (DTG) was as effective at blocking viral replication as combination ART in individuals treated within 180 days of infection. After the study period of 48 weeks, there was no significant difference in the incidence of DRMs between the two treatments, suggesting that DTG monotherapy could be viable [37]. However, it has been noted in the WHO HIV drug resistance report 2024 that levels of DTG resistance is increasing beyond levels anticipated in clinical trials [28]. Despite this, WHO continues to recommend DTG as first- and second-line treatment. This is further supported by Pinto *et al.* [38] who found that DTG resistance was not transmitted to individuals who had yet to receive any treatment, allowing it to remain a reliable first-line medication. Regardless, there is the possibility that more DRMs specific to DTG will arise as there are multiple known mechanisms of drug resistance in other INSTI class drugs [39]. To counteract the upward trend of DRMs, an increasing body of research is being directed towards alternative methods of treating HIV infection.

A third barrier to developing a cure for HIV which needs to be mentioned here is the lack of robust animal models which replicate the course of viral infection in a similar pattern to humans, thus hampering the transition of preclinical research to human clinical trials. This is due to the high level of host specificity exhibited by the HIV virus [40] typical of the retrovirus family. Nonhuman primates (NHPs) infected with the closely related Simian Imuunodeficiency Virus have been the most established models for HIV research and have been central in preclinical trials of HIV treatments [41], but there are key differences between the pattern of SIV in NHPs and HIV in humans which such models do not address [40]. These issues have been addressed by, for example, establishing genetically modified NHP models using CRISPR/Cas9 gene editing technologies to replicate the impact of human genetic factors on infection outcome [41] or genetically modified strains of HIV virus which can infect NHPs, thereby better replicating the course of HIV infection that occurs in humans [40]. However, this does not circumvent the considerable ethical issues, cost implications and complex management of using NHPs in research [42, 43]. Therefore, there

is considerable effort to develop murine models of HIV infection as a possible solution to widening the choice of animal models for HIV preclinical research, including establishing transgenic mice to replicate particular HIV associated pathologies [43, 44]. An area which has made considerable recent progress is the development of humanized mouse models by engrafting immunodeficient mouse strains with human cells or tissues, which can replicate the pattern of HIV infection and immune responses seen in humans [40]. These include the "Bone Marrow/Liver/Thymus (BLT) humanized mouse model" [40] which have been used extensively to investigate HIV viral latency, and have been key in developing some of the novel research approaches towards finding a cure to HIV outlined in the next section.

3 Research Towards Finding a Cure for HIV

3.1 *CCR5* Δ32 Mutation

In 2007, the first case of an apparent cure for HIV was discovered in Berlin [45]. Timothy Ray Brown received a bone marrow transplant to treat acute myeloid leukaemia (AML), after which all the latent HIV-infected cells were destroyed and replaced with the stem cells from the donor [45]. The donor selected by the research team had a rare mutation of the *CCR5* gene, where both alleles had the *CCR5* Δ32 mutation [45]. The *CCR5* gene encodes the CCR5 chemokine receptor, one of the cell surface co-receptors that HIV binds to in order to be taken into the cell [45]. However, the homozygous *CCR5* Δ32 mutation prevents this protein from being expressed so the host cell is resistant to HIV [45]. Consequently, Brown no longer required ART and was HIV-free until he passed away as a result of his leukaemia in 2020 [45]. This procedure was replicated successfully on two other AML patients in London and Düsseldorf, bringing the total number of cured cases to three [45]. Furthermore, a recent study from Hsu *et al.* [46] reported the first potential case of a cured female. Interestingly, the patient received a haplo-cord transplant, not a bone marrow transplant. The transplanted cells were a combination of homozygous *CCR5* Δ32 umbilical cord blood cells and haploidentical adult stem cells [46]. A limitation of the original method was the rarity of *CCR5* Δ32/Δ32 mutations and the need for a complete match between donors and recipients [45], but cord blood cells are able to engraft even with partial matches [46]. This development may allow more patients to undergo the curative procedure and makes the *CCR5* Δ32 mutation a clear target for further research.

Despite its successes, harnessing utilisation of the *CCR5* Δ32 mutation as a treatment option raises some concerns. As a chemokine receptor, CCR5 plays a role in host cell interactions with a range of viruses, not just HIV [47]. The absence of CCR5 receptors has been found to increase the risk of severe West Nile virus and lethality rate of influenza [47]. Studies conducted on mice found that CCR5 deficiency worsened stroke-related brain injuries and patients also had lower natural killer cell levels, potentially affecting bone growth and development [48]. Additionally, stem cell transplants come with significant risks and potential side effects, such as graft versus host disease which can be fatal, so are only suitable treatments for patients with serious blood disorders [49]. Furthermore, receiving *CCR5* Δ32/Δ32 stem cells does not guarantee a permanent HIV cure [50]. A case known as the "Essen patient" was seemingly cured by the absence of CCR5, but the HIV virus rapidly re-replicated soon after the treatment, via the alternative CXCR4 co-receptor that was not present in transplants given to the previously described cases [50]. HIV most commonly utilises the CCR5 receptor in the initial infection but in 50% of cases, this can later develop into the late-stage CXCR4-tropic virus over time [51]. While it is understood that an initial infection by the CXCR4-tropic virus is possible, there is less priority in developing CXCR4-focused treatment due to the low incidence of these viruses [51]. However, CXCR4-tropic HIV strains are associated with faster disease progression and Marichannegowda *et al.* [52] identified a case of CXCR4-tropic transmission in a patient with the wild type *CCR5* gene, supporting the need for more research into CXCR4-tropism in HIV. There is currently no documented *CXCR4* gene mutation that has as significant an effect as *CCR5 ⊿32*, so research on stem cell transplants has focussed on the latter. While it would be informative to trial this treatment on more patients, a scoping review found the total cost of stem cell transplantation studies to range from 60 to 700 thousand US dollars [53]. As an alternative, gene editing technologies such as CRISPR

have been used in in vitro and ex vivo studies, but the technique still requires more development before it can be implemented in vivo [54].

3.2 "Shock and Kill" Method

An alternative approach, the "Shock and Kill' method, aims to directly target latent HIV infected cells that are not cleared by conventional ART treatment. As highlighted earlier, ART has to be administered for life otherwise the reservoir of latent HIV-infected cells reactivates as soon as ART treatment is stopped. The "shock and kill" method aims to overcome viral latency by using latency reversing agents (LRA) to "shock" latent cells into activation [55]. Once the latent reservoirs are transcriptionally active, they can be detected and killed by the immune system and current ART drug regimens [55]. Theoretically, the HIV infection could be cured if the latent cells were eradicated from the body, removing the risk of reactivation and viral replication [55].

Table 1: *Classes and Mechanisms of Latency Reversing Agents. Table to show the main classes of current LRAs Latency Reversing Agents in trial and the molecular pathways they target in order to increase HIV transcription and/or viral production. Abbreviations as follows: P-TEFb, positive transcription elongation factor b; TLR, Toll-like receptor; mTOR, mechanistic target of rapamycin; STAT5, signal transducer and activator of transcription 5; IL-15, interleukin-15. Adapted from Kim, Anderson, and Lewin [61].*

Latency Reversing Agents (LRA)	
Classes	**Molecular Pathways Targeted**
Epigenetic Modifiers	• Histone deacetylase inhibitors • Methylation inhibitors • Methyl-transferase inhibitors • Bromodomain inhibitors • P-TEFb activators
TLR Agonists	• TLR7 • TLR9
Protein Kinase C Agonists	• Prostratin/Bryostatin • Ingenol B/PEP005
NFκB Agonists	• Smac mimetics
PI3K/Akt Pathway	• Disulfram • STAT5 signalling benzotriazole • mTOR complex rapamycin
TCR Activators	• Immune checkpoint blockers
Unclassified	• Quinolines • Cytokines IL-15

There are a variety of current LRAs being investigated that target different mechanisms of cell latency, summarised in Table 1. The most widely used approach has been to to modify the host's chromatin to upregulate transcription [55-57]. Histone deacetylases (HDAC) condense chromatin and inhibit transcription so LRAs using HDAC inhibitors (HDACi) are a potential mechanism for preventing cells from going into a latent state [55]. HDACi are delivered to target cells within oxygen-containing nanosomes, as HDACi are less effective in low oxygen levels. A study by Hong *et al.* [58] incorporated both HDACi and protein kinase A activators in a nanosome and found that it could induce transcription of HIV. However, while combination LRA treatments have shown promising activity in in vitro models with reactivated cells producing HIV-RNA, proteins and releasing active viral particles, in vivo studies have not supported these results. While a number of candidate LRAs have been evaluated in animal models and

early preclinical trials, although there was a time-limited increase in levels plasma and cellular levels of HIV RNA transcripts detected, most studies showed no detectable effect on the size of the latent HIV reservoir [56, 57]. For example, while LRAs such as HDACi were able to increase overall HIV RNA transcripts in vivo, they did not increase the multiply-spliced RNA which is necessary for HIV protein translation and viral replication [57]. The reason for the lack of correlation is likely due to the multiple mechanisms that operate in vivo the maintain HIV latency which are not fully replicated in vitro. Studies show cells carrying HIV-1 proviruses can be located in a broad range of tissue reservoirs vary widely in their susceptibility to LRAs [56, 59]. Susceptibility to LRAs in vivo is likely to be influenced by the impact of genetic and epigenic factors and interaction with viral components; there are potentially multiple possible integration sites for the HIV provirus DNA which have be observed in vivo which are not recapitulated in vitro [56]. Another issue is that memory T cells are mainly dormant in nature so the forcibly activated cells may not have enough cytosolic components and transcription factors to supply the upregulated viral transcription at a detectable level [60]. In this case, it is possible that LRAs would simply promote replication of the latent cells, and the immune system would be unable to downregulate transcription effectively [56, 57]. Rebound viral replication may be more severe after ART is stopped with the assumption that HIV was fully eradicated from the body [60]. Some studies in primates have also indicated that LRAs can increase levels of pro-inflammatory cytokines with the risk of CNS damage [57, 59].

3.3 "Block and Lock" Method

An alternative approach to "Shock and Kill" strategies is the "Block and Lock" method. This approach aims to use Latency Promoting Agents (LPA) to block transcription until an epigenetic silencing "lock" is established, preventing a significant rebound viral replication after the cessation of ART [62]. Any minute amounts of viral replication could then be disposed of by the immune system so lifelong treatment would no longer be necessary [59]. As with LRAs, LPAs can take a variety of approaches due to the complexity of the transcription processes involved [59]. One target is the HIV accessory protein Tat as it is expressed in the host cells from early on in infection, and is well conserved across HIV-1 strains. Tat is actively released by infected cells and is able to penetrate other cells, inducing viral transcription by facilitating the release of P-TEFb in infected cells. The effect of Tat on uninfected cells is less studied, but it is suggested that Tat leads to oxidative stress and DNA damage in B cells [63]. Tat inhibition directly stops viral production with no alternatives in the HIV pathway [59].

Moranguinho and Valente [59] identified didehydro-Cortistatin A (dCA) as a potential Tat inhibitor with in vitro studies showing long-term use resulted in a state of latency that was unresponsive to LRAs and persisted after treatment was discontinued. In vivo studies on mice also showed a decrease in viral RNA and slower rebound viral replication when ART was interrupted [59]. When injected intraperitoneally into mice, dCA was able to cross the blood-brain barrier [59]. This is important as microglial cells, the main types of resident macrophages found in the brain, are also targets for HIV viral latency [64]. However, LPAs have yet to be approved for clinical use due to cytotoxicity and limited efficacy. Huang *et al.* [65] proposed the use of ponatinib, a drug that inhibits HIV transcription through the AKT-mTOR pathway and is already approved as a clinical treatment for leukaemia. No major drawbacks have been identified in this method, but further studies are necessary before it can be implemented clinically. A comparison of the key differences between the "Shock and Kill" and "Block and Lock" approaches for targeting HIV viral latency are briefly summarised in Table 2.

Table 2: *A comparison between the "Shock and Kill" and "Block and Lock" approaches for targeting HIV viral latency. The key differences between these two strategies are briefly summarised. Data drawn from a range of sources [56, 57, 59].*

	"Shock and Kill"	**"Block and Lock"**
Mechanism	Reactivates HIV latently infected cells	Inactivates HIV latently infected cells
Mediated by	Latency-reversing agents (LRAs)	Latency promoting agents (LPAs)
Objective	Render all HIV-infected latent cells transcriptionally active, allowing detection by the immune system and/or ART drug regimens. Once all latent cells are eradicated from the body the remaining virus can be eliminated by ART.	Lock HIV transcription until epigenic silencing is established in all HIV-infected latent cells; reduce viral replication to residual amounts which can be targeted by the immune system
Potential risks/ side effects in vivo	Some LRAs induce proinflammatory responses	Some LPAs showed levels of cytotoxicity
Additional Notes	Promising in vitro studies but limited efficacy observed in vivo to date	Promising in vitro studies but limited efficacy observed in vivo to date

3.4 Vaccination

An alternative approach is to attempt to harness active HIV-neutralising B cell and $CD4^+/CD8^+$ T cell responses through generating an effective vaccine against HIV. However more than 40 years into the HIV pandemic, there is still no licensed vaccine available in the foreseeable future, despite extensive research [66]. Developing an effective vaccine to HIV presents major challenges; unlike influenza and SARS-CoV-2 vaccines it is essential that the vaccine can prevent infection, not just reduce symptom severity [67]. Other barriers are the extensive sequence diversity in the HIV Env protein, the rapid establishment of viral latency soon after infection and the need to trigger adequate immunity at the mucosal surface of the reproductive tract, the main site of viral colonisation [66]. Additionally, live attenuated vaccines carry the risk of permanent infection [67].

A few vaccine candidates have made it to early-stage clinical trials. An HIV vaccine candidate known as SAV001-H was generated by the research team of Dr. Chil-Yong Kang [68] using a "whole-attenuated virus" approach. The HIV virus was genetically manipulated to remove the *nef* gene responsible for pathogenicity, followed by chemical treatment and gamma irradiation. The attenuated virions were able to trigger the production of HIV specific neutralising antibodies while eliminating any risk of infection or viral replication. Studies showed no serious side effects and antibody production was significantly increased and maintained across the 52-week study period [68]. However, to date this vaccine has not progressed to phase 2 clinical trials, and no HIV vaccine candidates have progressed to phase 3 [66].

Other HIV vaccine strategies have included adenovirus vectors, recombinant peptides, and DNA vaccines. Liposome particle technology based on a range of immunogens derived from the HIV Env and other proteins, and mRNA technology is also being explored [66]. A notable vaccine candidate was the Mosaico (HVTN 706) vaccine developed by Janssen, which incorporated a wide range of HIV epitopes delivered with an adenovirus vector to encourage an immune response against multiple HIV variants [69]. However, the phase 3 trial was discontinued in 2023 as it was found to be ineffective in preventing HIV infection [70]. The PrEPVacc study in Africa involved 2 different combinations of recombinant peptide and DNA vaccines [69], but it was also discontinued due to the lack of efficacy [71]. Many current studies on HIV vaccines, including Mosaico and PrEPVacc, were designed to induce the production of non-neutralising antibodies and give rise to a $CD8^+$ T cell response upon infection, but did not induce any effective cytotoxicity in humans [72].

A number of vaccine candidates aim to induce the production of broadly neutralising antibodies (bNAbs) capable of binding multiple variants of the HIV virus preventing entry into target cells. Some vaccine candidates with this mechanism target the highly conserved domains in the Env glycoprotein, such as the fusion peptide (FP), membrane proximal external region (MPER) and CD4-binding site (CD4bs) [73, 74]. Rujas *et al.* [73] studied the potential of liposome-based vaccines containing FP-MPER hybrid peptides. This successfully produced bNAbs in rabbits, but levels were low due to poor immunogenicity [73]. A study in macaques were able to elicit bNAbs in response to CD4bs-like (CD4 binding site-like) proteins in a lipid nanoparticle vaccine, but this was only elicited after six immunisations which is not representative of a typical vaccine regime [74]. Another vaccine candidate utilised mRNA technology to induce the production of virus-like particles (VLPs) through Env-Gag glycoprotein mRNA within lipid nanoparticles, which triggered the production of antibodies to VLPs and HIV antigens. Testing in macaques and mice has been effective and a phase 1 clinical trial is expected to begin in early 2024 [75].

While the successful development and implementation of a vaccine raises the possibility that HIV could be more readily controlled or even eradicated [66], the barriers to generating an effective HIV vaccine are multifold and largely concern the immune evasion mechanisms of the virus [76, 77]. The latent viral reservoir which persists in an infected individual (summarised in the Introduction on p.5-6), means the virus is effectively hidden from both ART treatment and from the immune system. Another barrier in generating a functional immune response to HIV has been the difficulty in eliciting effective and long-lasting BNAbs to the viral Env protein. While up to 30% of HIV-1 individuals generate antibodies which cross-react with more than one strain of HIV virus only a very small proportion generate antibodies capable of fully blocking transmission [76, 78]. Contributing factors include the complex maturation process of these antibodies in humans, interference by immune tolerance mechanisms and the presence of a glycan shell on the HIV virus gp120; glycans tend to have low immunogenicity. These factors are compounded by the high level of heterogeneity and mutation rate seen in the HIV virus, particularly in its Env protein, and the need to generate effective mucosal immunity [78]. The challenges in developing an effective animal model capable of accurately replicating human immune responses to the HIV virus, also highlighted in the Introduction, is another compounding factor contributing to the failure of promising preclinical trials to migrate into the clinical stages [40, 77].

3.5 Passive immunization with bNAbs

A related approach to vaccination which has made recent progress is the possibility of generating effective bNAbs in vitro or in vivo, and administering them to humans as passive immunotherapy against the HIV virus. Although the challenges in stimulating functional bNAbs have been summarized in section 3.4, effective bNAbs have been identified and characterized in HIV-infected individuals. The first bNAb to the HIV Env protein was isolated from an asymptomatic HIV-1 infected patient in 1994, and since then many different classes of effective bNAbs, targeting conserved areas of the Env protein which mediate HIV attachment to host cells, such as the CD4 binding site, have been isolated and characterized [79]. Initial preclinical studies in non-human primates demonstrated administration of bNAbs significantly reduced viral load and delayed a rebound in infection, but early clinical trials only showed only short-term effects in humans [79]. However, with increased development in the technologies for isolation and generation of monoclonal antibodies suitable for preclinical and clinical use, more effective immunotherapies have progressed from preclinical to early clinical trials. The most promising progress is the use of a combination of two or more bNAbs, or combining bNAbs with ART, giving long-lasting suppression of viral load in HIV-1 infected individuals [80-82]. For example, a recent clinical trial using a combination of three bNAbs showed effective viral suppression in the majority of HI-infected individuals for the duration of treatment in the absence of ART [81]. Although these approaches would be better classified as new treatment or preventative approach rather than a strategy towards HIV cure, recent trials in SHIV infected rhesus monkeys demonstrated that bNAb immunotherapy could be combined with latency-reversing agents

(LRAs) to successfully aid elimination of the viral reservoir, and some of these approaches are in early clinical trials in HIV infected individuals undergoing ART [79].

4 Discussion

A theoretical cure for HIV could encompass both individual treatments and/or widespread eradication of the virus. Of the research strategies highlighted here, the "Block and Lock" method utilising Tat inhibition is potentially the most promising due to the well conserved nature of the Tat protein across HIV mutant strains. Unlike the "Shock and Kill" method, there is no risk associated with the insufficient cytosolic components in the latent cells, and this approach is unlikely to increase the severity of a viral rebound if the treatment is unable to permanently silence HIV replication. Administering LPAs would be simpler, safer, and cheaper than stem cell transplantation, and could be incorporated into existing ART regimens or combined with passive bNAb immunotherapy [79]. Another newly developing approach is the first CRISPR human gene editing treatments which have only just been approved within the UK in 2023 for certain genetic blood disorders [83]. To date, only one CRISP-Cas9 approach (EBT-101), designed to excise HIV proviral DNA, has had some success in eliminating latent SIV DNA in non-human primates and has been approved for clinical trials [84], and there is potential to use CRISPR-Cas9 technologies to modify CCR5 in stem cells for potential autologous transplantation [59]. However, as well as the issue of cost, the use CRISPR-Cas9 technology for human or viral genome editing raises multiple ethical issues, regarding safety, potential off-target effects producing negative effects on other parts of the genome, issues with informed consent for use of germ cells, and the potential for environmental harms or misuse, which are all major barriers to the implementation and uptake of these treatments[85, 86].

As well as the barriers that come from the biology of the virus itself, the other barriers developing a widely available cure for HIV are socio-economic and ethical issues. Currently, people living with HIV have higher healthcare costs and healthcare utilisation over time: a study in the US showed people living with HIV had on average healthcare costs of $34,643- $47,105 per individual over a 5-year period [87], although costs can be reduced by migrating to single-tablet regimens in countries where this is an economically viable alternative [88]. Lifelong treatment with ART is estimated to cost €126,317 -€254,964 ($133,201-$268,859) [89]. With potential HIV cure treatments in the research phase, it is difficult to estimate specific costs, but a number of factors suggest these could be significantly more expensive than current ART at least in the early phases of development. These factors include the complexity and duration of treatment, limited availability resulting in higher costs due to limited production and/or distribution, as well as costs associated with regulation and development. Vaccines are highlighted as one of the most cost-effective healthcare interventions for the prevention of infectious disease [90], especially if tiered pricing is applied to increase their global accessibility [91] and could potentially be more economically viable for widespread use than lifelong ART. The COVID-19 pandemic prompted an expansion in vaccine technologies, but also highlighted some of the ethical concerns over distribution and application of vaccination regimens. Widespread eradication of HIV by vaccination would require the vast majority of the population to be vaccinated to achieve herd immunity, but mandatory vaccination would infringe on patient autonomy [92]. The considerable barriers to effective vaccine development have already been highlighted (Section 3.4) and they come with a high burden of developmental costs. For instance, one of the more recent (to date) HIV Phase 1 vaccine trials, HIVTN702, was quoted as costing over $100million USD and availed no protection [77].

Critically, the greatest burden of HIV is in the sub-Saharan African region [1] where inadequate economic and healthcare resources already struggle to prevent transmission and treat current patients. It can be argued that the resources used to implement novel treatments in wealthier countries should instead be used to increase the availability of current preventative measures and treatments in countries with lower incomes. The sub-Saharan African region is heavily reliant on philanthropic organisations to research and distribute resources to control HIV, when it could be argued that this region should be prioritised in receiving HIV

control measures to have the greatest impact on eradicating HIV [93]. For an HIV cure strategy to be functional in the sub-Saharan African region, it would need to be more economical than current lifelong ART regimens and easy to administer [94]. Unless an effective vaccine can be developed, the "Block and Lock" or "Shock and Kill" approaches, in conjunction with other interventions such as passive transfer with BNAbs, currently seem to be the most promising if they can be rendered effective in vivo. Developing more effective in vitro and animal models of latent HIV infection would aid the development of these strategies [17]. While the range of promising new approaches summarised here suggest that a cure for HIV or preventative vaccination could be developed in the foreseeable future, this cannot be detached from the gamut of ethical concerns which need to be acknowledged and appropriately navigated [85, 92].

5 Conclusions

There are many potential approaches to developing a cure to HIV, and while this review doesn't attempt to cover all the current studies, we highlight some of the main pathways being investigated. Each of these approaches show some hopeful prospects in its unique way. While more research and trials are needed, the progress in scientific advancements raises the hope that a cure to HIV can be developed and bring the possibility of eventually eliminating this virus. Currently, as the spread of HIV mutations threaten to reduce the effectiveness of current ART treatment, we would hope to see such research prioritised in an attempt to curb this 40+ year old epidemic. The "Block and Lock" approaches appear to be the most viable in terms of an individual cure if they can be rendered effective in vivo, as the target is well-conserved across DRMs and medication would be cheaper and safer than transplants or gene editing, in conjunction with passive transfer with BNAbs and/or ART regimens. While vaccination would be the most economically viable approach, research efforts spanning decades have yet to produce a viable vaccine. Ethical debates raise valid concerns over whether allocating resources to funding research into HIV cure strategies would have greater overall benefit than increasing access to testing and treatments in lower-income areas, such as the sub-Saharan African region where HIV is most prevalent. Regardless of the approach taken, the global threat of HIV has driven widespread research efforts, suggesting a halt to the HIV epidemic could be a possibility in the foreseeable future, provided that socio-economic, ethical and virus-specific barriers can be navigated.

6 Declarations

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6.2 Competing Interests

The authors of this work have no competing interests.

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