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Understanding the Barriers to HIV Cure: A Scoping Review of Recent Literature

Nana Ansua Ababio[1], Bright Ansah Adjei[2]

Christiana Michael Akpan[3], Maame Achiaa Adu-Kofi[4], Jacob Narteh Kodji[5], Karl Osei Afoduo[6], Raymond Kwesi Matey[7], Alberta Afua Kekeli Ayebi[8], Nana Adwoa Dsane[9]

[1,3,8]Medical Officer, University of Ghana Medical Centre
[2,6,7]Senior Health Research Officer, University of Ghana Medical Centre
[4]Medical Officer
[5]Internal Medicine Resident, 37 Military Hospital
[9]Dep. Director of Research, University of Ghana Medical Centre

Abstract
Human Immunodeficiency Virus (HIV) continues to be a global health challenge, with an estimated 42 million people projected to be living with the virus by 2030. Since the report of a cure for HIV after C-C chemokine receptor type 5 Δ32 stem cell transplantation 16 years ago, no other case of HIV cure has been reported despite significant research and advances in antiretroviral therapy (ART). This review explores the barriers responsible for making it difficult to achieve a cure for HIV.

Keywords: HIV Cure Barriers, Latent Viral Reservoir, Antiretroviral Therapy (ART)

Introduction

According to the World Health Organization (WHO), HIV has claimed about 42.3 million deaths as of July 2024. Out of 39.9 million people living with HIV in 2023, 65% were living in the WHO African Region (WHO, 2024). Although antiretroviral therapy (ART) has made significant strides in rendering HIV a manageable chronic condition, it is not a cure (Abana et al., 2022; Chun et al., 2015). The persistence of the latent viral reservoir - dormant proviruses integrated into the host genome – poses the primary barrier to a cure (Siliciano & Siliciano, 2021). The proviruses hide and evade both ART and the immune system, reactivate upon treatment cessation and are capable of reigniting active infection (Lichterfeld et al., 2022; Ho et al., 2013). After decades of research for a cure, HIV cure remains elusive, hindered by scientific, biological, and socioeconomic challenges (McColl et al., 2018; Katlama et al., 2013). This scoping review explores the key barriers to achieving HIV cure, including the persistent latent reservoir, biological and immunological factors, scientific and technical challenges, and socioeconomic and global health inequalities (Rossouw et al., 2017).

The latent reservoir, often likened to a "hidden intruder," is the most formidable obstacle, as current strategies like gene editing and "shock and kill" struggle to eliminate or silence these dormant proviruses (Siliciano & Siliciano, 2021). Unfortunately, inadequate tools to measure the HIV reservoir and the

biological diversity of HIV subtypes complicate cure efforts, particularly in low- and middle-income countries (LMICs) where non-B subtypes dominate (Rossouw et al., 2017). Socioeconomic barriers, such as inadequate access to advanced diagnostics, frequent ART interruptions, and high rates of co-infections like malaria and tuberculosis, further exacerbate the challenge. Promising HIV cure strategies, including immunotherapy and gene editing, are often impractical in resource-limited settings, highlighting the need for scalable and affordable solutions. Basic discovery research and clinical trials in resource-limited settings must be strengthened and will require enabling infrastructure development and capacity building. Moreover, scientists' lack of consensus on a unified cure approach has fragmented research efforts, slowing progress toward a cure (Deeks et al., 2021).

In this review, we aim to provide an understanding of the barriers bedeviling HIV cure research and the need for a collaborative global effort to overcome them. By addressing these barriers, the scientific community can move closer to achieving a cure that benefits all populations, regardless of geographic or socioeconomic status (Deeks et al., 2021; Rossouw et al., 2017).

Methods

This scoping review aimed to identify the key barriers to achieving HIV cure in recent literature. A narrative approach was employed to provide an overview of the literature on the topic, following the Arksey and O'Malley framework (Rossouw et al., 2017). We systematic search was conducted using two electronic databases, PubMed and Google Scholar, with the following search terms: "barriers to HIV cure," "HIV cure," and "latent reservoir." The search was limited to studies published between 2010 and 2025 to ensure relevance to current research trends. From PubMed, 515 articles were initially identified, of which 24 were deemed relevant after title and abstract review. After further screening, 3 articles were excluded; 1 article was not focused on HIV cure barriers whereas the other 2 articles were not written in English. This resulted in a final selection of 21 articles from PubMed. From Google Scholar, 68 results were retrieved, out of which only 4 articles met the inclusion criteria after removing 64 duplicates. Finally, a total of 25 articles were included in this review. We included articles that focused on barriers to HIV cure and provided insights into latent reservoir or cure strategies. Non-English papers were excluded from this review.

The selected papers were analyzed and organized into themes. Using a narrative synthesis approach, we interpreted and summarized study findings, highlighting areas of consensus and disagreement. While this review provides a comprehensive overview of barriers to HIV Cure, its limitations include selection bias due to its narrative approach and the exclusion of non-English studies. Regardless, this paper provides insights into the barriers to HIV cure. This review did not require any ethical approval because this was not human subjects research.

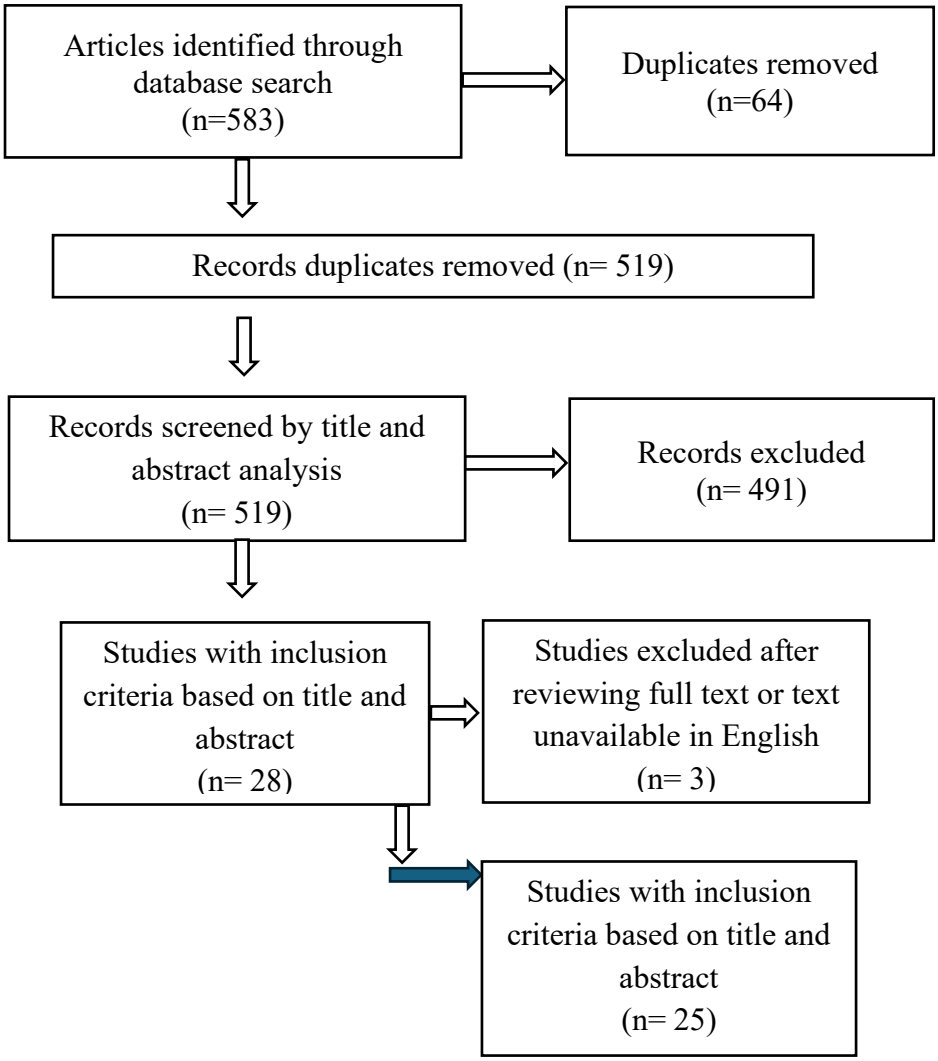

Figure 1: A flow diagram of the articles reviewed

Current Barriers to HIV Cure

Persistent Latent Reservoir

Persistent latent reservoir is the primary reason why there is no cure for HIV yet (Pitman et al., 2018). When HIV infects a person, the virus inserts its genetic material into the DNA of immune cells, creating a hidden copy called a provirus. While majority of the viruses actively replicate, some proviruses enter a dormant state, hiding in tissues and long-lived memory called CD4+ T cells. The dormant proviruses are invisible to both antiretroviral therapy (ART) and the immune system, which only targets active viruses. For illustration, ART serves as a security system that stops burglars (active viruses) but cannot detect a hidden intruder (dormant provirus) already inside the house. If ART is stopped, the dormant proviruses can "wake up," leading to viral rebound and the return of active infection. People living with HIV must therefore take ART for life to keep the virus suppressed (Pitman et al., 2018; Tomar et al., 2018; Margolis et al., 2020).

Strategic efforts to eliminate the latent reservoir, including the "shock and kill" approach, aim to wake up dormant proviruses so that drugs like ART can destroy the infected cells. However, the approach currently faces significant challenges. Not all proviruses are reactivated - some remain hidden - and the latency reservoir is highly diverse, with proviruses hiding in different cell types and tissues like the gut, lymph

nodes, and the brain (Cossarini et al. 2024; Abana et al., 2022; Castro-Gonzalez et al., 2018; Pitman et al., 2018; Katlama et al., 2013; Lewin et al., 2011). This makes it nearly impossible to target every dormant provirus. Imagine trying to clean a house infested with cockroaches, even if you spray one room, cockroaches in hidden cracks or playing dead will survive and repopulate the house later. Until scientists find a way to destroy every dormant provirus - or keep them asleep forever in latency – the HIV virus will always have a way to rebound (Abana et al., 2022; Siliciano & Siliciano, 2021; Chun et al., 2020).

Scientific and Technical Challenges

Another major barrier in the fight for HIV cure is accurately measuring the replication-competent reservoir - the pool of dormant but functional proviruses capable of reigniting infection. According to Ho et al. (2013), current HIV cure strategies have limitations because the quantitative viral outgrowth assay (QVOA), considered the gold standard, underestimates the reservoir as it only detects proviruses that can be reactivated in the lab, and not those that remain stubbornly dormant. Also, tests that measure total HIV DNA overestimate the reservoir by including defective proviruses - genetically damaged viruses that cannot replicate (Ismail et al., 2021). This discrepancy makes it difficult to evaluate the effectiveness of cure strategies, as researchers cannot precisely determine how much of the reservoir has been eliminated. To illustrate, visualize trying to count the number of working light bulbs in a warehouse filled with both broken and functional bulbs. A test like QVOA only counts the bulbs that light up when you flip the switch, missing the ones with faulty switches that could still work if repaired. Meanwhile, a total HIV DNA test counts every bulb in the warehouse, including the broken ones, giving an inflated number. Neither method gives the true count of functional bulbs, making it hard to know how many need to be replaced.

Clonal Expansion

Another complication in the fight for HIV Cure is clonal expansion, where infected cells multiply by creating the same copies of themselves. This happens through homeostatic proliferation (normal cell maintenance) or as a response to immune triggers (antigen-driven responses) (Pitman et al., 2018; YC et al., 2013). The cloned populations act as the virus "backup", to ensure its survival even if some infected cells get eliminated. Ho et al. (2013) argue that if one cell in a clone is destroyed, its “identical siblings” can still produce new viruses, making complete eradication of the virus nearly impossible. The clonal expansion is analogous to a dandelion spreading in a garden. Even if you pull out one dandelion, its seeds (clones) may have already spread, and new plants may grow elsewhere. Similarly, cells infected with HIV can multiply and spread rapidly, making it difficult to eliminate the virus completely.

Viral Diversity

In addition, viral diversity poses a significant challenge for HIV cure research. HIV is not a single virus but a family of subtypes, with subtypes A, C, and D being predominant in low- and middle-income countries (LMICs), unlike subtype B, which is more common in high-income countries and the focus of most cure research (Ismail et al., 2021). These subtypes differ in key areas, such as the activity of the viral promoter (LTR), the function of the Tat protein (which regulates viral replication), and pathways to drug resistance (Abana et al., 2022). For instance, subtype C viruses are known to exhibit higher transcriptional activity, but faster silencing of the viral promoter compared to subtype B (Rossouw et al., 2017). These differences mean that a cure strategy optimized for subtype B may not work for other subtypes. This draws attention to the need for subtype-specific research, especially in LMICs where the HIV burden is highest. HIV subtypes may be perceived as different car models. A repair manual designed for a sedan (subtype B)

might not work for a truck (subtype C) due to differences in engines and other parts. Similarly, a cure strategy tailored for one HIV subtype may not work for another, requiring customized approaches for each.

Biological and Immunological Factors

The ability of HIV to persist in the body is largely influenced by viral proteins like Tat and Nef, which play critical roles in immune evasion, latency, and reservoir dynamics. The Tat protein acts as a "switch" that turns on viral replication by binding to the virus's genetic material. Researchers have found that some of the HIV subtypes, for example subtype C, have a Tat protein (TatC) that is more active than others, potentially making it harder to keep the virus dormant (Rossouw et al., 2017). Nef protein on the other hand help HIV-infected cells evade the immune system by hiding them from detection. According to Ismail et al (2021) Nef can reduce the display of viral proteins on the surface of infected cells, making them invisible to immune cells. These proteins vary across HIV subtypes, meaning the behaviour of the latent reservoir may differ depending on the subtype a person is infected with. For illustration, assume Tat and Nef as a virus's "stealth toolkit." Tat is like a remote control that can turn the virus on, while Nef is like a cloaking device that hides infected cells from the immune system. HIV subtypes have slightly different versions of these tools, which can affect how well the virus hides and how easily it can be controlled.

Another important factor is the role of immune activation and inflammation in shaping the reservoir. When the immune system is constantly activated (as it is during untreated HIV infection), it creates more target cells for the virus to infect, helping the reservoir grow. Pitman et al. (2018) also report that even after starting ART, some people continue to have high levels of inflammation, which is linked to a larger reservoir and poorer health outcomes.

Additionally, researchers have argued that sex differences also play a role as women tend to have higher levels of immune activation and faster disease progression than men, even at similar viral loads (Ismail et al., 20212; Gianella et al., 2016). By implication, cure strategies, such as drugs targeting the immune checkpoint protein PD-1, may work differently in women compared to men. For example, PD-1 agonists, which have shown promise in reactivating latent HIV in men, may not be as effective in women due to differences in immune responses (Ismail et al., 20212; Gianella et al., 2016). The immune system is analogous to a security team trying to control an uprising (HIV infection). In women, the riot might be more intense (higher inflammation), and the security team's tools (like PD-1 agonists) might not work as well as they do in men. This means that cure strategies need to be tailored to account for these differences. Since immune activation and inflammation are known to differ between the sexes, detailed studies into the immune correlates of reservoir size in males and females are needed. Ismail et al. (2021) reported a difference in the immune correlates between males and females in PLWH in Uganda –In males the frequency of $PD\text{-}1^{+}\ CD4^{+}$ T cells and $IL\text{-}2^{+}\ CD8^{+}$ T cells were positive and negative correlates of replication-competent reservoir size, respectively, while only $TNF^{+}\ CD8^{+}$ T cells was found to have a positive association with replication-competent reservoir size in females. Other studies in men consistently link higher PD-1 levels to larger HIV reservoirs (the virus's hideouts in the body), this connection does not seem to hold for women. Since PD-1-blocking drugs were designed based on findings in men, there is a real risk these therapies—meant to 'smoke out' hidden virus—might not work the same way for women. This gap raises big questions about how we test immune-based treatments. To avoid leaving half the population behind there is the need to study these therapies in both men and women, and not just assume one size fits all" (Ismail et al., 2021:10).

Socioeconomic and Global Health Barriers

In LMICs, where HIV hits hardest, there are several challenges including diagnostic tools that hinder efforts to find a cure. Limited access to advanced diagnostics, like tests to measure the latent reservoir, makes it difficult to monitor the effectiveness of cure strategies (Rossouw et al., 2017). Also, issues like drug resistance, ART adherence, and co-infections like malaria and tuberculosis further complicate the situation. For instance, interruptions in ART due to socioeconomic barriers or supply shortages may lead to drug resistance, making it harder to control the virus and consequently reduce the pool of individuals eligible for HIV cure trials, which often require stable viral suppression (Ismail et al., 2021; Rossouw et al., 2017).

Another critical challenge is understanding the impact of co-infections and inflammation on the HIV reservoir. Co-infections like tuberculosis (TB), malaria, and hepatitis are common in LMICs and can increase immune activation and inflammation, potentially accelerating HIV progression and reservoir seeding (Rossouw et al., 2017). For example, TB co-infection has been shown to increase viral replication and immune activation, which could lead to a larger and more stable reservoir (Pitman et al., 2018). However, the interplay between co-infections, inflammation, and the HIV reservoir remains poorly understood. Studying these interactions is essential for developing cure strategies that work in real-world settings, where co-infections are a daily reality for many people living with HIV (Ismail et al., 2021).

Furthermore, many promising cure strategies, such as immunotherapy or gene editing, are costly and require sophisticated infrastructure, making them impractical for LMICs. Gene editing technologies like CRISPR-Cas9, which aim to cut HIV out of infected cells, require specialized labs and trained personnel, which are often unavailable in resource-limited settings. Also, immunotherapies that boost the immune system to target HIV-infected cells are expensive and difficult to administer (Rossouw et al., 2017). These barriers project the need for simpler, scalable, and affordable solutions that can be implemented in LMICs, where the HIV burden is highest.

Diverse Cure Strategies Without Clear Consensus

The lack of a unified agreement on HIV cure approach is also another reason why there is no cure for HIV yet. Scientists and researchers have pursued different strategies, such as "shock and kill" (reactivating dormant HIV to eliminate it), immune-based therapies (boosting the immune system to target HIV), gene editing (cutting HIV out of infected cells), and "block and lock" (permanently silencing the virus). Though each approach is promising, none has proven universally effective, and they all face challenges. For instance, the "shock and kill" approach struggles with incomplete reactivation of the latent reservoir (Siliciano & Siliciano, 2021), while gene editing is expensive and requires advanced infrastructure, making it impractical especially for low- and middle-income countries (LMICs) (Ismail et al., 2021). Without agreement on which strategy is most effective or feasible, resources and research efforts will be spread thin, slowing progress toward a cure because each approach remains potentially relevant (Pitman et al., 2018).

To overcome these barriers, a more collaborative, global effort is needed. This includes prioritizing scalable, affordable, and subtype-specific solutions, as well as addressing the unique challenges faced by LMICs, such as limited access to advanced diagnostics and treatment interruptions. By aligning research priorities, standardizing metrics, and focusing on strategies that can be implemented globally, the scientific community can make faster progress toward a cure. Until then, the lack of agreement on a unified approach remains a key obstacle in the quest to end HIV (Pitman et al., 2018; Rossouw et al., 2017).

Discussion

The quest for HIV cure is one of the most formidable challenges in modern medicine, as highlighted by the persistent latent reservoir, scientific and technical hurdles, biological complexities, socioeconomic barriers, and diverse cure strategies. The latent reservoir, characterized by latent proviruses integrated into the host genome, is globally recognized as the primary obstacle to a cure (Abana et al., 2022; Lichterfeld et al., 2022; Chun et al., 2015). Whereas antiretroviral therapy (ART) effectively suppresses active viral replication, it cannot destroy hidden proviruses, which can reactivate upon ART cessation (Siliciano & Siliciano, 2021). This has led to the exploration of strategies like "shock and kill," immune-based therapies, and gene editing. However, as aforementioned, these cure strategies face significant limitations. For instance, the "shock and kill" approach struggles with incomplete reactivation of the reservoir (Siliciano & Siliciano, 2021), while gene editing, though promising, is highly expensive and logistically impractical for low- and middle-income countries (LMICs) (Rossouw et al., 2017). These challenges underscore the need for novel solutions that can effectively target the latent reservoir without relying on complex or resource-intensive methods.

A critical point of debate noteworthy is the lack of consensus on a unified cure approach among scientists and researchers. While some researchers advocate for "shock and kill" due to its potency to eliminate reactivated proviruses, others argue for "block and lock," which aim to permanently silence the virus. According to Katlama et al. (2013) this approach would be more feasible and conducive in resource-limited settings. This divergence reflects the complexity of HIV biology and the varying priorities of funding agencies and researchers. While the American Gene Technologies blog highlights the challenges of eradicating the latent reservoir, Springer reviews highlight the need for affordable and scalable solutions tailored to LMICs (Rossouw et al., 2017). These differing perspectives reveal a fragmented research landscape, where resources are spread thin across multiple strategies without a clear path forward. The lack of coordination not only slows progress but also risks leaving behind populations in LMICs, where the epidemic is severe. Additionally, Seberi et al. (2022) expresses the need to engage young people living with HIV (YLWH) in cure research as they will soon be at the forefront of decision making toward ending the HIV pandemic.

Another area of significant challenge in HIV cure is adequately measuring the latent reservoir. Current methods, such as quantitative viral outgrowth assay (QVOA) and total HIV DNA tests, have notable limitations. Studies have shown that QVOA tends to underestimate the reservoir by detecting only proviruses that can be reactivated in the laboratory, thereby missing those that remain dormant, while tests that measure HIV DNA (such as PCR (qPCR)-based assays, Intact Proviral DNA Assay (IPDA)) typically overestimate the reservoir by including defective proviruses which are incapable of replication (Ho et al., 2013; Pitman et al., 2018). Functional assays like Tat/Rev Induced Limiting Dilution Assay (TILDA) also measure inducible HIV RNA but miss latent viruses that fail to activate under lab tests. These inconsistencies complicate cure strategies and highlight the need for standardized, reliable assays (Siliciano & Siliciano, 2021) as several approaches have proven inadequate.

Also, the biological diversity of HIV subtypes adds another strain of complexity. Most cure research focuses on subtype B, which is prevalent in high-income countries, but LMICs face subtypes A, C, D, and recombinants with distinct biological properties (Ismail et al., 2021; Pitman et al., 2018; Rossouw et al., 2017). For instance, subtype C viruses exhibit higher transcriptional activity, but faster silencing of the viral promoter compared to subtype B, which potentially affects efficacy of latency-reversing agents (Rossouw et al., 2017). This subtype-specific variability underscores the need for more inclusive research

that addresses the unique challenges faced by LMICs (Pitman et al., 2018).

Generally, this review has revealed that socioeconomic and global health barriers also complicate the pursuit of HIV cure. Limited access to advanced diagnostics, frequent ART interruptions, and high rates of co-infections like tuberculosis and malaria in LMICs create additional barriers for the fight against HIV (Rossouw et al., 2017). These factors not only aggravate the HIV epidemic but also limit the applicability of cure strategies developed in high-income settings. Gene editing and immunotherapy, for instance, while promising, may not be feasible in LMICs as they require sophisticated infrastructure and are often impractical in resource-limited settings. These constraints highlight the need for simpler, scalable, and affordable solutions that can be implemented globally (Pitman et al., 2018). Moreso, the impact of co-infections and inflammation on the HIV reservoir remains poorly understood, yet these factors are critical to developing effective cure strategies in real-world settings (Ismail et al., 2021).

Conclusion

In summary, the lack of agreement on a unified cure approach, combined with scientific, biological, and socioeconomic challenges, has significantly hindered progress toward HIV cure strategies. To overcome these barriers, a more collaborative, global effort is needed - one that prioritizes scalable, affordable, and subtype-specific solutions while addressing the unique challenges faced by LMICs. By aligning research priorities, standardizing metrics, and fostering international cooperation, the scientific community can accelerate progress toward a cure that benefits all populations, regardless of geographic or socioeconomic status. Until then, the latent reservoir and its associated challenges will remain the greatest obstacle in the quest to end HIV.

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