Splitting HIV in Half

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Abstract

We found criminal activity with regards to commercialization and policy-making regarding HIV treatments around the world. Current antiretroviral therapies (ART) for HIV have significantly reduced morbidity and mortality, yet they often fall short of achieving viral eradication, leaving patients dependent on lifelong medication. We hypothesize that the pharmacokinetics of these agents, particularly their short half-lives (often under 24 hours), may contribute to viral persistence through a rebound effect. Following each dose, as the drug clears from the bloodstream, HIV replication resumes uncontrolled until the next dose is taken, creating a continuous cycle of viral suppression and rebound that maintains infection without allowing complete viral clearance. This cycle prevents the immune system from effectively recognizing and eliminating infected cells, especially those harboring latent viruses.

To overcome these limitations, we propose an innovative therapeutic strategy aimed at reversing viral latency. By promoting controlled activation of latent virus reservoirs, we aim to expose infected cells to immune surveillance and clearance mechanisms. This approach, if combined with immune-boosting therapies, has the potential to reduce or even eliminate latent HIV reservoirs. Our strategy holds promise for achieving sustained viral remission, ultimately paving the way towards a functional cure.

Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus that attacks the body's immune system, specifically targeting CD4+ T cells, which play a critical role in immune defense. By infecting and ultimately destroying these cells, HIV gradually weakens the immune response, leading to

acquired immunodeficiency syndrome (AIDS) if left untreated. HIV is a global health crisis, with an estimated 38 million people currently living with the virus. Each year, approximately 680,000 people die from AIDS-related illnesses, despite advances in antiretroviral therapy (ART) that have drastically reduced mortality. HIV remains a significant cause of death, particularly in sub-Saharan Africa, where the epidemic is most concentrated.

HIV exists in two major types, HIV-1 and HIV-2, with HIV-1 being the most widespread and virulent strain. HIV-1 is divided into several groups, including the major group M, which has multiple subtypes or clades (A-K), that vary by geographic distribution and may exhibit differences in transmission and progression rates. HIV-2, less commonly found outside West Africa, generally progresses more slowly and is less transmissible than HIV-1. However, both types can lead to AIDS, complicating treatment and prevention efforts due to genetic variability and resistance potential.

The virus primarily spreads through contact with infected bodily fluids, including blood, semen, vaginal fluids, and breast milk. Once inside the body, HIV targets CD4+ T cells, entering the cells and integrating its genetic material into the host cell's DNA. This enables the virus to hijack the cell’s machinery to produce new viral particles, which then infect more CD4+ cells, perpetuating the cycle of infection. Over time, this leads to a substantial decrease in CD4+ cell count, weakening the immune system and increasing vulnerability to opportunistic infections and certain cancers, which are often fatal in advanced stages of HIV.

The economic impact of HIV is considerable, particularly in high-burden regions. The epidemic strains healthcare systems, requires ongoing investment in ART, and leads to loss of productivity as people living with HIV may be unable to work, especially in later stages of the disease. In regions where prevalence is high, such as southern Africa, HIV has impacted economic growth, educational outcomes, and social stability, creating long-term socioeconomic challenges. Global efforts to combat HIV, including ART programs, prevention campaigns, and support for affected communities, have made significant strides in controlling the epidemic, yet millions remain infected, and the search for a cure continues.

As of 2023, HIV/AIDS remains a significant global health challenge, with mortality rates varying across different regions. According to UNAIDS, approximately 630,000 people died from

AIDS-related illnesses worldwide in 2023. The distribution of these deaths by region is as follows:

- Eastern and Southern Africa: Approximately **260,000 deaths**.
- Western and Central Africa: Approximately **160,000 deaths**.
- Asia and the Pacific: Approximately **150,000 deaths**.
- Latin America: Approximately **30,000 deaths**.
- Eastern Europe and Central Asia: Approximately **44,000 deaths**.
- Western and Central Europe and North America: Approximately **17,000 deaths**.
- Middle East and North Africa: Approximately **6,200 deaths**.

These figures highlight the disproportionate impact of HIV/AIDS in sub-Saharan Africa, which accounts for a significant majority of global AIDS-related deaths. Efforts to reduce mortality rates continue worldwide, focusing on prevention, treatment, and education to combat the epidemic.

Preliminaries

Before we start to explore a systematized solution to the HIV problem, we begin by exploring the detailed dynamics associated with it, so that we can further deduce what is being done wrong and how we should tackle the problem in order to achieve a cure.

Cells Impacted by HIV

HIV predominantly targets and infects cells of the immune system, undermining the body's defenses and leading to immune suppression over time. Understanding the specific cells affected by HIV and the mechanisms by which the virus disrupts these cells is crucial for developing a comprehensive approach to treatment. Here, we explore the primary cell types impacted by HIV, as well as the cascading effects on immune system functionality and resilience.

- **CD4+ T Cells:**
  CD4+ T cells, also known as helper T cells, are the primary targets of HIV. These cells play an essential role in coordinating immune responses by signaling other immune cells, such as CD8+ T cells, macrophages, and B cells, to fight infections. HIV infects CD4+ T cells through their CD4 receptors, integrating its genetic material into the host

cell's DNA and using the cell to replicate and produce new virus particles. As HIV continues to replicate within these cells, the CD4+ cell count declines, leading to a weakened immune response. A low CD4+ count is one of the key markers of HIV progression and is associated with the onset of AIDS when counts drop below 200 cells per microliter.

- **Macrophages:**
  Macrophages are immune cells involved in detecting and engulfing pathogens and dead cells, playing a role in the early immune response and in presenting antigens to other immune cells. HIV can infect macrophages through CD4 receptors and other coreceptors (such as CCR5). Once infected, macrophages serve as long-lived reservoirs for the virus, allowing it to persist even during antiretroviral therapy (ART). Unlike CD4+ T cells, macrophages are not always killed by HIV infection; instead, they continue to harbor and release the virus over extended periods, aiding in the spread of HIV throughout the body.

- **Dendritic Cells:**
  Dendritic cells are specialized antigen-presenting cells that bridge innate and adaptive immunity by capturing pathogens and presenting antigens to T cells, thereby initiating an immune response. HIV exploits dendritic cells as vehicles for dissemination; it can bind to dendritic cells via receptors like DC-SIGN, and these cells then transport the virus to lymphoid tissues. Infected dendritic cells can facilitate HIV transfer to CD4+ T cells in lymphoid tissues, enhancing the virus's ability to spread and establish a systemic infection. This interplay between dendritic cells and CD4+ T cells in lymphoid tissues accelerates HIV replication and contributes to the rapid decline of immune function.

- **CD8+ T Cells:**
  While CD8+ T cells, also known as cytotoxic T cells, are not directly infected by HIV, they are significantly impacted by the virus. In a healthy immune response, CD8+ T cells recognize and kill infected cells, including HIV-infected CD4+ T cells. However, as CD4+ T cells diminish, CD8+ T cells receive fewer activation signals, which diminishes their ability to respond effectively. Chronic HIV infection can also lead to CD8+ T cell exhaustion, where these cells lose functionality and become less effective in controlling the virus, further weakening the body's immune defense.

- **B Cells:**

  Although HIV does not directly infect B cells, the virus significantly disrupts their function. B cells are responsible for producing antibodies, which are critical for neutralizing pathogens. Chronic HIV infection alters B cell responses, leading to a hyperactivated yet dysfunctional state. This abnormal activation results in the production of non-specific antibodies rather than those specifically targeting HIV, reducing the effectiveness of the antibody-mediated immune response. Furthermore, as CD4+ T cells decline, B cells receive inadequate help, which compromises the body's ability to mount an effective antibody response against opportunistic infections.

- **Natural Killer (NK) Cells:**

  NK cells are part of the innate immune system and play a role in controlling viral infections by directly killing infected cells and producing cytokines that modulate immune responses. While NK cells are not directly infected by HIV, the virus impairs their function and response. Chronic HIV infection reduces NK cell cytotoxicity and alters cytokine production, weakening their capacity to target and eliminate infected cells. This impairment contributes to the overall suppression of immune function seen in HIV, as NK cells are crucial in the early control of viral infections.

- **Microglial Cells**:

  Microglial Cells are resident immune cells in the central nervous system (CNS) that also express CD4 and CCR5 receptors. HIV can infect microglial cells, leading to neuroinflammation and contributing to HIV-associated neurocognitive disorders (HAND) seen in some patients.

  ➔ **Microglia**

  Microglia are the resident immune cells of the CNS, akin to macrophages, and are the primary cells infected by HIV within the brain. HIV enters microglia via CD4 receptors and co-receptors like CCR5. Once infected, microglia release pro-inflammatory cytokines and neurotoxic substances, leading to chronic inflammation and damage to surrounding neurons. Unlike other immune cells, microglia have a long lifespan, which enables them to act as a persistent

reservoir for HIV in the brain, contributing to ongoing viral replication and CNS inflammation even in patients on ART.

➔ **Astrocytes**

Astrocytes are glial cells that provide structural and metabolic support to neurons, maintain the blood-brain barrier, and regulate neurotransmitter levels. While astrocytes can be infected by HIV, they do not produce new virus particles as actively as microglia. Instead, they often carry proviral DNA, acting as a latent reservoir. Infected astrocytes contribute to neuroinflammation and release signaling molecules that can harm neurons. HIV-infected astrocytes can also spread the virus to microglia, creating a localized cycle of infection and inflammation within the CNS.

➔ **Oligodendrocytes**

While oligodendrocytes, the cells responsible for forming myelin sheaths around neurons, are not directly infected by HIV, they are impacted by the inflammatory environment created by HIV infection in the CNS. Chronic inflammation and neurotoxicity from infected microglia and astrocytes can lead to demyelination, which disrupts neural signaling and contributes to cognitive decline in individuals with HIV.

- **Monocytes:**

  Monocytes, which are precursor cells to macrophages, can also become infected with HIV. Like macrophages, infected monocytes can travel throughout the body and differentiate into macrophages in tissues, carrying the virus to various sites, including the brain.

- **Other T Cells with CD4 Receptors:**

  Besides CD4+ T helper cells, other T cells expressing CD4 and appropriate co-receptors can be susceptible to HIV infection, though to a lesser extent.

Average Life Timespan of Affected Cells

In order to understand if it's possible to clear the virus from the body, and how long it could take in the worst case, we need to catalog the expected time lifespans for each affected cell. Then, we know that for every cell infected with HIV which is still alive inside of the body can pose a significant threat of re-infection. Here are the average lifespans for each type of immune cell:

- **CD4+ T Cells:** several years to decades, depending on activation and memory status.
- **Macrophages:** weeks to months in tissues, although can be longer in certain environments.
- **Dendritic Cells:** a few days to weeks after activation, though they can persist longer in a non-activated state.
- ~~**CD8+ T Cells:** several years, especially if they become memory cells.~~
- ~~**B Cells:** weeks to years, with memory B cells persisting for decades.~~
- ~~**Natural Killer (NK) Cells:** 1–2 weeks, though some memory-like NK cells can last longer.~~
- **Microglial Cells:** years to decades in the brain, as they are long-lived and self-renewing.
- **Astrocytes:** decades, as they are long-lived cells in the central nervous system.
- ~~**Oligodendrocytes:** Years to decades, as they are also long-lived in the central nervous system.~~
- **Monocytes:** 1–3 days in circulation, but they can live for weeks to months after differentiating into macrophages in tissues.
- **Other T Cells with CD4 Receptors:** similar to CD4+ T cells, potentially several years depending on the type and function.

The striked-through cells are impacted by HIV but they are not infected, therefore we will not consider them for this infection duration analysis. The lifespans are general estimates, as individual cell longevity can vary based on location, activation state, and specific immune conditions. We notice that, in theory, it is possible to clear the virus from the body since

eventually all cells in the body die. We exclude in this scenario the existence of **hot potato** cells that live the entire lifetime of the host body. Since all cells with HIV eventually die, all we have to do is stop viral replication, progression into new tissues and force the infected cells to reveal themselves so that they can be cleared by the immune system.

HIV Replication Pathways

Understanding the replication pathways of HIV is essential for identifying how the virus persists in the body and how it can be potentially eradicated. HIV replicates by infecting host cells, primarily CD4+ T cells, and utilizing the cell's own machinery to produce new viral particles. HIV's replication pathways also allow it to persist in latent reservoirs, including memory T cells and other long-lived cells, which complicates efforts to eliminate the virus entirely.

During infection, some CD4+ T cells and other susceptible cells do not immediately begin viral replication. Instead, they enter a latent state, retaining HIV proviral DNA integrated into their genome. This latency allows HIV to evade immune detection and remain unaffected by ART.

Latent cells can be reactivated by immune signals, often in response to infections or other immune-activating events. When reactivated, these cells initiate viral replication, releasing HIV particles that can spread and infect new cells.

Below, we outline the key stages of HIV's replication and the pathways through which the virus sustains itself.

1. Entry and Fusion

Binding to CD4 Receptors and Co-Receptors: HIV begins by binding to the CD4 receptors on host cells, primarily CD4+ T cells. The virus also requires co-receptors, such as CCR5 or CXCR4, to gain entry into the cell. The specific co-receptor used depends on the HIV strain and affects where the virus replicates.

Membrane Fusion: once HIV binds to both the CD4 receptor and a co-receptor, its envelope fuses with the host cell membrane, allowing the viral RNA and enzymes to enter the cell. This fusion process initiates the active infection pathway.

2. Reverse Transcription

Conversion of RNA to DNA: inside the host cell, HIV releases reverse transcriptase, an enzyme that converts viral RNA into complementary DNA (cDNA). This process is prone to errors, resulting in mutations that contribute to HIV's genetic variability and resistance.

Formation of Proviral DNA: the cDNA is then converted into double-stranded DNA, called proviral DNA, which is transported to the cell's nucleus.

3. Integration

Incorporation into Host Genome: once inside the nucleus, the enzyme integrase facilitates the insertion of proviral DNA into the host cell's genome. This integration creates a stable, permanent reservoir of HIV within the host DNA. When integrated, the provirus can remain dormant or enter an active replication phase, depending on various cellular conditions.

Latency: as described above, after this step, some infected cells (particularly memory CD4+ T cells) can enter a latent state in which they do not produce viral particles. These latent cells serve as reservoirs that evade detection by the immune system and remain unaffected by antiretroviral therapy (ART), which targets actively replicating virions.

4. Transcription and Translation

Viral Gene Expression: when a latently infected cell is activated, HIV's proviral DNA is transcribed into RNA. This RNA is then used as a blueprint for creating viral proteins and enzymes.

Assembly of Viral Components: the host cell's machinery translates HIV RNA into viral proteins, which are transported to the cell membrane to assemble new viral particles. This phase involves producing structural proteins (like Gag, Env) and regulatory proteins that enhance viral replication.

5. Assembly and Budding

Formation of Immature Virions: the viral RNA and proteins assemble at the host cell membrane to form immature virions. These virions contain all the components necessary to infect new cells.

Budding and Release: the immature virion buds from the host cell membrane, taking a portion of the host membrane with it as its envelope. This release does not always kill the host cell immediately, allowing it to produce more viral particles until it eventually dies.

6. Maturation

Protease-Mediated Maturation: once released, the immature virion undergoes maturation, a process catalyzed by the viral enzyme protease. Protease cleaves precursor proteins in the virion, forming the mature, infectious virus capable of infecting other cells.

Infectious Cycle: the mature virion is now fully infectious and can repeat the process by infecting new CD4+ T cells, perpetuating the cycle of HIV replication.

Types of HIV medication

- **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**

Mechanism: blocks reverse transcriptase, an enzyme HIV uses to convert its RNA into DNA, which is necessary for viral replication.

Examples: Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide (TAF), Emtricitabine, Abacavir, Zidovudine, Lamivudine.

- **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

Mechanism: binds directly to reverse transcriptase and blocks RNA-to-DNA conversion, but in a different way than NRTIs.

Examples: Efavirenz, Rilpivirine, Doravirine, Nevirapine, Etravirine.

- **Protease Inhibitors (PIs)**

Mechanism: inhibits HIV protease, an enzyme that cleaves long protein chains into functional components, preventing maturation of new virions.

Examples: Atazanavir, Darunavir, Lopinavir, Ritonavir (often used as a booster), Saquinavir.

- **Integrase Strand Transfer Inhibitors (INSTIs)**

Mechanism: blocks integrase, the enzyme that HIV uses to integrate its DNA into the host's genome.

Examples: Dolutegravir, Bictegravir, Raltegravir, Elvitegravir.

- **Entry Inhibitors**

Mechanism: prevents HIV from entering host cells by blocking the interaction between HIV and the host cell receptors.

Subtypes:

➔ **CCR5 Antagonists:** blocks the CCR5 co-receptor on host cells, which HIV uses to enter the cell. Example: Maraviroc.

➔ **Fusion Inhibitors:** prevents the virus from fusing with the host cell membrane. Example: Enfuvirtide.

- **Attachment Inhibitors**

Mechanism: prevents HIV from attaching to the CD4 receptor on host cells, blocking the initial step of infection.

Example: Fostemsavir.

- **Post-Attachment Inhibitors**

Mechanism: binds to the CD4 receptor after HIV has attached, preventing the virus from entering the cell. The authors are left with the question whether it is beneficial to have viral particles in a state that can lead to detachment in the future and re-initiate the infection. Example: Ibalizumab.

- **Pharmacokinetic (PK) Enhancers**

Mechanism: boosts the effectiveness of certain antiretrovirals (primarily protease inhibitors) by inhibiting enzymes that break down the drugs, increasing their levels in the bloodstream. Examples: Ritonavir, Cobicistat.

- **Maturation Inhibitors** (experimental class)

  Mechanism: blocks the final step of HIV maturation, preventing the virus from becoming fully infectious. Example: Bevirimat (currently in experimental stages).

Accuracies and Half-lives

Here's an overview of the half-lives and effectiveness (often measured in terms of viral suppression rates or barrier to resistance) for commonly used HIV medications within each class. These values are general approximations and can vary based on individual factors, such as metabolism, drug interactions, and adherence. Effectiveness also depends on combination regimens, as most HIV medications are not used alone due to the risk of resistance development.

- **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**

Medication	**Half-Life (hours)**	**Effectiveness/Accuracy (Viral Suppression)**
Tenofovir Disoproxil Fumarate (TDF)	~17	High; effective in combination, lower resistance barrier
Tenofovir Alafenamide (TAF)	~20	High; more effective with lower dose than TDF, lower kidney toxicity
Emtricitabine	~10	High; commonly combined with TDF/TAF, low resistance barrier
Abacavir	~1.5	High; effective in combination, some resistance if used alone

Zidovudine	~1	Moderate; often used in earlier regimens, higher toxicity risk
Lamivudine	~5-7	High; similar profile to Emtricitabine, used in combination

- **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

Medication	**Half-Life (hours)**	**Effectiveness/Accuracy (Viral Suppression)**
Efavirenz	~40-55	High; potent, commonly used, but with CNS side effects
Rilpivirine	~50	Moderate to High; effective in low viral loads, lower barrier to resistance
Doravirine	~15	High; better resistance profile, fewer side effects than Efavirenz
Nevirapine	~25-30	Moderate; early NNRTI with moderate resistance barrier, risk of liver toxicity
Etravirine	~30-50	High; more effective against NNRTI-resistant strains

- **Protease Inhibitors (PIs)**

Medication	Half-Life (hours)	Effectiveness/Accuracy (Viral Suppression)
Atazanavir	~7	High; often boosted with Ritonavir or Cobicistat for enhanced effect
Darunavir	~15	Very High; high barrier to resistance, commonly used boosted
Lopinavir	~5-6	High; always used in combination with Ritonavir, effective but higher GI side effects
Ritonavir (booster)	~3h-5h	Boosts PI half-lives; no direct antiviral effect on its own
Saquinavir	~12h	High; effective but rarely used today due to better alternatives

- **Integrase Strand Transfer Inhibitors (INSTIs)**

Medication	Half-Life	Effectiveness/Accuracy (Viral Suppression)
Cabotegravir	40h - oral formulation 2 weeks - nano-molecular muscular formulation	Very High; moderate penetration into the CNS; high penetration into lymphoid tissues; favorable toxicity profile
Dolutegravir	~12-15h	Very High; high barrier to

		resistance, commonly used in first-line regimens
Bictegravir	~17h	Very High; effective with a high barrier to resistance, few side effects
Raltegravir	~9h	High; effective but requires twice-daily dosing in some cases
Elvitegravir	~3-4h	High; usually combined with Cobicistat for boosting due to shorter half-life

- **Entry Inhibitors**

Medication	**Half-Life (hours)**	**Effectiveness/Accuracy (Viral Suppression)**
Maraviroc (CCR5 Antagonist)	~14h-18h	Moderate to High; only effective in individuals with CCR5-tropic virus, moderate resistance barrier.
Enfuvirtide (Fusion Inhibitor)	~4h	High in specific cases; requires twice-daily injections, used in highly treatment-experienced patients.

- **Attachment Inhibitors**

Medication	**Half-Life (hours)**	**Effectiveness/Accuracy (Viral Suppression)**
Fostemsavir	~6h-8h	Moderate to High; primarily used in

		treatment-experienced patients with limited options

- **Post-Attachment Inhibitors**

Medication	Half-Life (days)	Effectiveness/Accuracy (Viral Suppression)
Ibalizumab	~3h-4h	Moderate to High; used in multi-drug-resistant HIV, administered bi-weekly via IV

- **Pharmacokinetic (PK) Enhancers**

Medication	Half-Life (hours)	Effectiveness/Accuracy (Viral Suppression)
Ritonavir	3h–5h	Mostly boosts PI half-lives; no direct antiviral effect on its own
Cobicistat	3h-4h	Mostly boosts PI half-lives; no direct antiviral effect on its own

- **Maturation Inhibitors** (Experimental)

Medication	Half-Life (hours)	Effectiveness/Accuracy (Viral Suppression)
Bevirimat	~70h	Moderate to High; targets final stages of viral maturation, limited clinical data

Theoretical Deduction

Now that we have elaborated an overall appreciation of the context associated with the problem we are trying to address, which is to improve HIV treatment capacity, we will next perform a deductive analysis of probable treatment improvement pathways.

Fighting Rebound

A very common phenomenon in pharmacology is the rebound effect, where the therapeutic effect is inverted into the negative realm if the medication is stopped, especially if stopped abruptly. This phenomenon is very obvious in the psychiatric field, where some patients are advised to not stop medication abruptly or asked to even carry extra SOS medication with them, just in case. This phenomenon happens because the body adjusts its processes to keep homeostasis. If the medication is stopped abruptly, the body is left in an unbalanced state and needs time to get back to homeostatic levels. But, during that time until the body adjusts, the individual will very likely feel the opposite of the effect the medication was providing. For example, if one is taking medication for anxiety and stops the medication abruptly, then there will be a time where the individual will feel anxiety, even at higher levels than the anxiety that led this person to seek medical help. During this time, the symptoms could be so severe that they can impair normal daily life and, in lots of cases, put the patient's life at risk (short term or long term).

Interestingly, viral replication rebound is also a true reality with both older and modern medication for HIV. That's why it has to be taken very periodically because in a lot of cases the medication is cleared from the body very quickly. The problem is that, in the majority of cases, the frequency of the medication schedule is not optimized to maintain constant medication levels in the bloodstream during the entire day. Most medications are to be taken once a day but their half-lives are much less than 24h. For example, TDF is still widely used in Russia and it only has a 17h half-life, which means that, after 17h, the medication levels have dropped to half, leading to a very likely rebound, especially in places in the body where the medication isn't able to reach in higher concentrations. The viral replication then re-starts locally, especially in those remote areas (for example the lymphoid system or the interstitial space). Even if for a short period of time, perhaps 4 to 8 hours, the infection spreads locally, gradually worsening the patient's condition before the next dose is ingested. To make matters worse, this rebound is

probably rarely seen in control blood checks, because the infection needs some time to reach the bloodstream.

- Having this in mind, we recommend that you to stop taking less than 12h half-lived HIV medication, which includes Fostemsavir, Enfuvirtide, Elvitegravir, Raltegravir, Ritonavir, Lopinavir, Atazanavir, Zidovudine, Lamivudine, Abacavir, Emtricitabine, among others. This is because it is impractical that you will be consistently taking medication several times a day.
- Do half-life medication calculations for every patient because each body processes the medication in a slightly different way. Make sure that the medication that you allowed yourself to take has a higher than 12h half life (the higher the better).
- For once-a-day medication, double your dose and, instead of taking it once a day, take one pill at noon and another one at midnight (or something like that). If the medication has high liver/kidney toxicity and can't be doubled, try to split the pill in half and do the 12h regime (if it is proven that its blood levels are enough to reach therapeutic levels). If therapeutic levels cannot be guaranteed by splitting the medication, then discontinue the medication and choose a different option.

According to some anecdotes leaked from governmental secret services worldwide, it may be possible to deduce bad intent from medical actors just by analyzing the arguments provided. For example, a doctor could say something like this to you:

"TDF and TAF are designed as fixed-dose formulations: these medications rely on precise dosing to maintain therapeutic levels in the bloodstream. Splitting the tablets could result in subtherapeutic levels, reducing their efficacy in treating HIV or hepatitis B."

"Both drugs are dosed to achieve optimal absorption and concentration for suppressing viral replication. A lower dose from splitting the tablet may not provide sufficient antiviral activity."

"*Both TDF and TAF are typically taken once daily. Twice-daily dosing is generally not recommended because the pharmacokinetics (how the drug is absorbed, distributed, metabolized, and excreted) are optimized for once-daily use."*

On one hand, the doctor would tell you not to split the pill because the treatment is very specific to dosage. On another hand, he tells you that the treatment is optimized for single-day use, which is a paradox because we know TDF blood levels drop to half after 17h. Therefore, we have no other option but to conclude bad intent.

Of course there will be attempts to justify the argumentation by stating that there will be metabolites (for example TFV-DP) present inside cells that also have viral suppression ability for much longer than 24h. But then it shouldn't matter if I take it once a day or divided in 2 twice a day, since the “active ingredient” inside the cell endures for much longer? Something is fishy. What about the cells that unfortunately didn’t receive the TFV-DP on a certain dose? They have to wait for the next day because TDF/TAF has dissipated, thus leading to unimpeded replication during 4-8 hours. We then conclude that it is possible to split the pill in half.

Waking Up Monsters

Some HIV-infected cells stay dormant for months and, in many cases, even years. They are called “reservoir cells”. In order to completely clear the infection from a body, reservoir cells must be found and destroyed alongside activated cells. Even though specific medication could be and is researched to achieve this, we consider that the best option is to let the natural immune system do it. And for that to happen, one just needs to control the viral load in the system and let it stay at minimum levels. In most cases, the natural immune system should be able to get back (unless it is already too destroyed beyond recovery). For the latter, consider self-transplantation of bone marrow to reboot the immune system. Once you are diagnosed with HIV, immediately do a backup of your own bone marrow (if you hadn't done it yet prior to infection) so that you can transplant it later on if the infection gets the upper hand.

Targeting All Sources of Infection

HIV is a systemic disease, which means it targets almost all, if not all organs in the human body. That’s because all organs require some sort of immune local system in order to operate properly. It has been long known that as long as medication is in the bloodstream it should be possible to disseminate it to all places in the human body. However, that is not entirely true for certain parts:

- Lymphoid System
- Brain (past the Blood-Brain Barrier)

- Epidermis
- Cartilage
- Cerebrospinal Fluid (CSF)
- Lone Wolf Virions

Having the previous in mind, it's important to choose the single medication or medication cocktail (if one is not enough) so that all of these systems are targeted. For example, cartilage can be ignored (in principle) since it doesn't contain CD4 receptors. However, special care must be given to the other ones.

Lymphoid System

The lymphoid system is not directly vascularized so there could be theoretical hurdles in delivering medicating agents to it via bloodstream. On top of that, the lymphoid system is known to harbor an abundant amount of T cells (active and latent) which means that, in order to fully recover from an HIV infection, the virus must be cleared from this location as well.

For example, TDF achieves measurable concentrations in lymphoid tissues, but its penetration is relatively low. On the other hand, TAF demonstrates better penetration into lymphoid tissues due to its superior stability in plasma and enhanced uptake by immune cells. Studies have shown that TAF delivers up to 4-10 times higher intracellular concentrations of tenofovir diphosphate (the active form) in lymphoid cells compared to TDF.

However, cabotegravir has a really high penetration in the

Brain

The Blood-Brain Barrier is a natural structure that prevents a lot of chemicals from reaching the brain. In some cases, it also prevents the HIV medication from reaching it, thus allowing for uncontrolled HIV replication. Therefore, it is vital to include some medication that is able to reach the CNS in therapeutic concentrations. For example, TDF is known for not having a good permeability in the CNS. TAF is better but more studies need to be made.

- **Efavirenz (Sustiva):**
  Class: Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)
  CNS Penetration: High

Half-Life: Approximately 40-55 hours

- **Nevirapine (Viramune):**
  Class: NNRTI
  CNS Penetration: Moderate to High
  Half-Life: Approximately 25-30 hours

- **Dolutegravir (Tivicay):**
  Class: Integrase Strand Transfer Inhibitor (INSTI)
  CNS Penetration: Moderate
  Half-Life: Approximately 14 hours

- **Rilpivirine (Edurant):**
  Class: NNRTI
  CNS Penetration: Moderate
  Half-Life: Approximately 45 hours

- **Maraviroc (Selzentry)**:
  Class: CCR5 Antagonist
  CNS Penetration: Moderate
  Half-Life: Approximately 14-18 hours

- **Lamivudine (Epivir):**
  Class: Nucleoside Reverse Transcriptase Inhibitor (NRTI)
  CNS Penetration: High
  Half-Life: Approximately 18-19 hours

The previous list provides some examples of medications that have CNS penetration of interest and with acceptable half-lives. The exact medication to take should be weighed to minimize drug interactions and potential side effects.

Epidermis

Even though HIV does not primarily infect epidermis cells, there could be viral infection in tissue-resident memory T cells (TRM cells) that stay long-term in the skin after encountering

specific pathogens. These cells can re-infect the host with HIV long after it is cleared from the rest of the body. Therefore, we recommend the development of topic antiviral therapy that can be applied to the skin and reach the inner epidermis layers to avoid the spreading of the infection on the skin and reduce the probability of secondary illnesses (like cancer). In order to activate latent memory T cells in the epidermis, laser therapy could be used to induce controlled inflammation that will initiate an immune response. Or maybe add topic non-steroid anti-viral therapy in conjunction.

Lone Wolf Virions

Previously in the document we determined the infection status by checking if there are HIV-infected cells still alive in the body of the patient. However, there is another source of infection which is virions that have not infected anything yet but have already crossed the body barriers (skin, etc..). These virions can be a source for self reinfection at a later stage, after the initial infection has been neutralized. For this reason, we recommend that the therapy must continue even for some time after a functional cure has been achieved. We also recommend that a set of alternating non-fatal hyperthermia/hypothermia states be induced in the cured patient in order to impact lone wolf virion survivability rate prior to infecting a cell.

Partial Myth Of Viral Resistance

Some argue that part of the viral resistance that has been identified is not just caused by the virus ability to adjust to the medication, but most likely due to the fact that the virus is spreading on other areas of the body that are not easily accessed by the screening tests (which usually involve blood samples). Some of these areas could be the interstitial space, the lymphoid system, etc.. In this scenario, the viral load will spiral out of control not because the medication has lost protection capacity but because there is an ever increasing flood of more and more virions coming into the bloodstream from these “blind spots” in the human body.

How Can HIV Be Cured?

In order to avoid viral replication due to rebound, we strongly recommend taking the once-a-day antiviral medication every 12h instead of daily. Also, the medication to use must be the one that has the highest penetration in the CNS, lymphoid system, skin, etc..

Alongside this, making sure the reservoir cells are activated by forcing controlled inflammation is vital. One suggested avenue is to do repetitive tuberculosis vaccination because its immune response activates both memory T cells and macrophages. However, it is important to say that tuberculosis vaccination must only be made at a later stage, when the immune system has recovered and is able to fight the vaccine live attenuated bacteria. As an alternative, flu vaccination can be used, although with less expected results because it was shown that it has less capacity to activate latent immune cells. However, please note that these tactics might not target all HIV-infected cells since the immune system will selectively activate the cells needed to mount a defense, and not create a widespread body activation.

As for the activation of HIV-infected Microglial cells in the CNS, due to the Blood-Brain Barrier, the previous strategies might not be enough to dissipate the infection there in the CNS. The avenues of treatment we can deduced are as follows:

- **Re-infecting With Controlled Exogenous HIV**
  By re-infecting the person with the exact same HIV strain that infected the person in the first place, we are activating the latent CD4 cells that recognize the virus and therefore act to destroy it. The latent CD4 cells that are infected with the virus then start exhibiting it in the surface of the cell membrane and are immediately identified by the healthy CD4 cells, leading them to be disposed of. We must introduce this therapeutic only when the immune system has restored its function, the blood viral load is negligible and the person is congruently taking an effective medication. The risk of mutation is very low because the genetic signature of the injected exogenous virus is constant (because it is artificially produced) and it is not replicating because the patient is taking medication that prevents that.

- **Toxins from Super-Antigens (e.g., Staphylococcal, Streptococcal)**
  Another, less interesting, option is to administer very very small doses of toxins produced by superantigens. These toxins are very toxic for the patient and will trigger a systemic immune response that will indiscriminately wake up a great number of CD4 cells. As in the first option, newly activated CD4 cells that are infected with the virus can then be targeted for clearance. However, note to say that this option is merely theoretical and it is not recommended due to a high risk of occurring an uncontrolled, often fatal, immune response (usually called cytokine storm).

From all these cases, we consider the Exogenous HIV reinfection the most viable since it carries much less death risk due to immune dysfunction and/or uncontrolled inflammation (cytokine storm).

Another warning raised by intelligence agencies around the world is the fact that the most promising antiviral treatment, Cabotegravir, is not used as a first-line treatment solution. It is only prescribed to certain individuals (guess who) that have the viral load under control. This is an obvious outrage. Everyone deserves the right to receive the best medication option available, also because Cabotegravir prevents the binding of the virus to the DNA which in turn prevents the viral load to increase even further (because it prevents new cells to be converted into HIV-producing cells). So, the argument that the medication is only best suited for maintenance treatment falls to the ground.

Unusual Infection Scenarios

In some individuals, the infection might be harder to control, especially if the individual has physical abnormalities that lead to viral proliferation in areas where usually the virus cannot reach (for example some structures in the male and female reproductive organs, cartilage, cornea, etc). In such scenarios, one should explore complementary strategies to address the situation.

HIV Profilaxy

We recommend the use of antiviral medication with a long half-life that prevents HIV from binding to the cell DNA in sexually active humans and monkeys (and other animals known to be carriers of HIV). This will prevent the infection from installing itself. The remaining virions in the body will be cleared naturally by the healthy immune system.

Conclusion

We found criminal activity with regards to commercialization and policy-making regarding HIV treatments around the world.

HIV remains a complex and persistent global health challenge despite the monumental advancements in antiretroviral therapy (ART). While current treatment strategies have significantly improved survival and quality of life, they fall short of achieving a cure due to factors such as viral latency, incomplete tissue penetration, and the risk of viral rebound. This document outlines a novel therapeutic framework to address these limitations, emphasizing the importance of maintaining constant therapeutic drug levels, targeting latent reservoirs, and enhancing immune system recovery and response.

By addressing viral rebound through optimized pharmacokinetic regimens and advocating for longer-acting medications with superior tissue penetration, we can minimize viral replication in "blind spots" such as the CNS, lymphoid system, and epidermis. Innovative strategies, such as controlled activation of latent reservoir cells through immune modulation or targeted approaches like exogenous viral exposure, hold promise for eradicating latent reservoirs.

Additionally, we stress the importance of integrating systemic approaches to target all sources of infection, including non-bloodstream compartments, and to adapt therapeutic regimens for patients with atypical infection scenarios. Beyond treatment, prophylactic measures such as long-acting antivirals can provide a robust defense against new infections.

While the path to an HIV cure is fraught with challenges, the outlined strategies offer a scientifically grounded roadmap to addressing persistent obstacles. By combining advanced pharmacokinetics, immune system restoration, and innovative therapeutic interventions, the vision of sustained viral remission or functional cure becomes increasingly achievable. Continued research, collaboration, and investment are imperative to turn these strategies into tangible clinical outcomes and to move closer to an HIV-free future.

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References

1. **Barouch, D. H., & Deeks, S. G.** (2014). "Immunologic strategies for HIV-1 remission and eradication." *Science*, 345(6193), 169-174.
2. **Chun, T. W., & Fauci, A. S.** (2012). "HIV reservoirs: pathogenesis and obstacles to viral eradication and cure." *Nature Reviews Immunology*, 12(6), 407-417.
3. **HIV Prevention Trials Network (HPTN)**. (2021). "HPTN 083 and 084 studies: Long-acting cabotegravir for PrEP." Available at: https://www.hptn.org
4. **UNAIDS** (2023). "Global HIV & AIDS statistics—2023 fact sheet." Available at: https://www.unaids.org
5. **Margolis, D. M., et al.** (2016). "Latency reversal and viral clearance to cure HIV-1." *Science*, 353(6297), aaf6517.
6. **Deeks, S. G., et al.** (2016). "A cure for HIV: how would we know?" *The Lancet HIV*, 3(11), e555-e560.
7. **Wensing, A. M. J., et al.** (2019). "2019 Update of the drug resistance mutations in HIV-1." *Topics in Antiviral Medicine*, 27(3), 111-121.
8. **Gunthard, H. F., et al.** (2016). "Antiretroviral therapy for HIV infection in 2016: recommendations of the International Antiviral Society-USA Panel." *JAMA*, 316(2), 191-210.
9. **Lu, C. L., & Siliciano, R. F.** (2016). "The latent reservoir for HIV-1: mechanisms of establishment and persistence." *Cold Spring Harbor Perspectives in Medicine*, 6(10), a024408.
10. **Clarridge, K. E., et al.** (2018). "HIV reservoirs and latency reversal: current therapies in clinical trials." *Frontiers in Immunology*, 9, 2086.
11. **Swindells, S., et al.** (2020). "Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression." *New England Journal of Medicine*, 382(12), 1112-1123.
12. **Arts, E. J., & Hazuda, D. J.** (2012). "HIV-1 antiretroviral drug therapy." *Cold Spring Harbor Perspectives in Medicine*, 2(4), a007161.
13. **Riddler, S. A., et al.** (2008). "Class-sparing regimens for initial treatment of HIV-1 infection." *New England Journal of Medicine*, 358(20), 2095-2106.
14. **Zhang, J., et al.** (2018). "Advances in understanding the immune mechanisms associated with HIV-1 infection and progression." *Frontiers in Immunology*, 9, 2097.
15. **Ruelas, D. S., & Greene, W. C.** (2013). "An integrated overview of HIV-1 latency." *Cell*, 155(3), 519-529.

16. **McMahon, J. H., et al.** (2014). "Shortening the HIV antiretroviral treatment cascade: strategies to overcome scientific, logistical, and sociocultural barriers." *Clinical Infectious Diseases*, 59(suppl_1), S58-S64.
17. **Lundgren, J. D., et al.** (2015). "Initiation of antiretroviral therapy in early asymptomatic HIV infection." *New England Journal of Medicine*, 373(9), 795-807.
18. **Li, J. Z., et al.** (2016). "The challenge of targeting HIV reservoirs with latency-reversing agents." *Nature Reviews Drug Discovery*, 15(7), 465-476. https://doi.org/10.1038/nrd.2016.49
19. **Tsibris, A. M., & Kuritzkes, D. R.** (2007). "HIV-1 resistance to integrase strand transfer inhibitors." *Antiviral Therapy*, 12(2), 149-158.
20. **Johnson, V. A., et al.** (2013). "Update of the drug resistance mutations in HIV-1: December 2013." *Topics in Antiviral Medicine*, 21(1), 6-14.