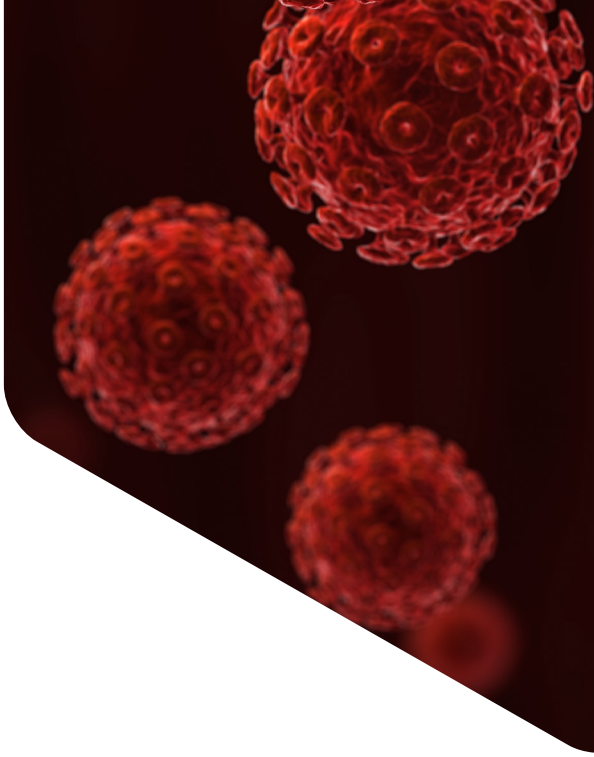

# Antiretroviral therapy advances and challenges: Bridging the gap to a functional cure

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Antiretroviral therapy advances and challenges

# HIV: A chronic health condition

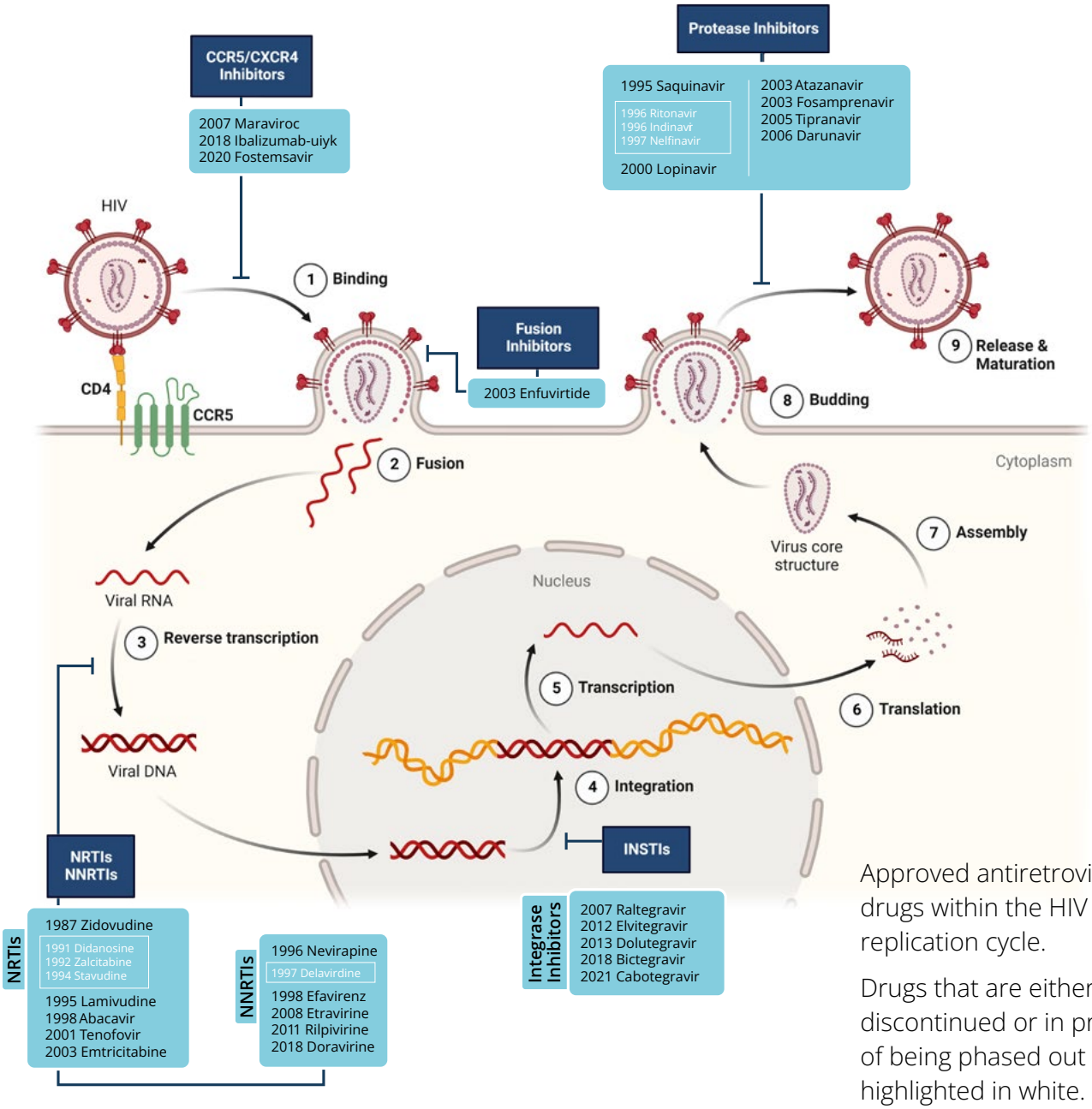
HIV/AIDs continues to be a major global health threat. Standard viral suppression treatments have largely rendered HIV infection a manageable, chronic health condition. However ongoing viral management is threatened by multiple challenges, including difficulties in managing long term treatment adherence, drug toxicity and development of drug resistance – any of which can lead to virological failure and disease progression. Current research into new therapies aims to mitigate these challenges through a combination of simplifying treatment regimens and developing more potent drugs targeting both existing and as-yet-unexploited targets.

Since the appearance of the first cases of AIDS in 1981, HIV infection has reached pandemic levels. Estimates suggest that there are currently more than 38 million people living with HIV worldwide, with 1.5 million new infections annually (1). Despite a still significant number of annual deaths, HIV has largely become a manageable, chronic health condition due to the development of antiretroviral drugs that actively suppress viral levels. AZT, approved in 1987, was the first. Additional drugs continued to be introduced the years that followed, leading to adoption in the 1990s of combination antiretroviral therapy (cART), also known as highly active antiretroviral therapy (HAART). HAART/cART employs a combination of three or more drugs which act against at least two different targets. Its adoption significantly reduced the number of AIDS-related deaths and quickly became the standard treatment – a situation that continues today, as newly diagnosed individuals are immediately placed on combination regimens.

Although there are hopes of developing a functional cure that would render HIV unable to cause illness in the absence of ongoing treatment, infected individuals today must follow a lifetime regimen of multiple drugs in order to maintain viral suppression. Research into new antiretroviral and other agents seeks to mitigate the challenges of ongoing, long term treatment, helping to provide a bridge to a functional cure.

Key events in discovery and evolution of HIV-1 therapy

| 1981 | 1982 | 1983 | 1987 | 1996 | 2006 | 2010 | 2018 | 2022 |
|---|---|---|---|---|---|---|---|---|
| Mysterious illness reported in 41 homosexual men by the New York Times | The term AIDS is created | HIV identified as the cause of AIDS | NRTI drug AZT is the first to be approved for AIDS | Introduction of protease inhibitors and the start of combination therapies | The first once-daily tablet, Atripla approved (TDF, emtricitabine and efavirenz) | Efficacy of cART increase from 43% in the mid 1990s to 78% in 2010*1 | The majority of patients worldwide eligible for ART are receiving them | Ongoing Phase 3 clinical trials of long acting formulations of potent, low toxicity cART, islatravir and lenacapavir |




Approved antiretroviral drugs within the HIV replication cycle.

Drugs that are either discontinued or in process of being phased out are highlighted in white.

*Illustration created with Biorender.com*

**Footnote *1**
The efficacy of combination antiretroviral therapy, currently referenced instead of HAART, increased from 43% in the mid 1990s to 78% in 2010, measured as their ability to maintain undetectable viral loads for a minimum of 48 weeks, when administered to patients with less than 100 000 copies/mL at the initiation of treatment.

# Approved antiretroviral treatments

Antiretroviral drugs target different phases of the HIV-1 replication cycle through a variety of mechanisms. The cycle begins with the virus binding to CD4+ T cells, and the HIV envelope then fuses with the CD4+ T cell membrane, enabling the virus to enter the cell. Once inside, the virus's capsid (a protective protein sheath) is disassembled, freeing the virus's packaged genetic material and enzymes needed for replication. Through reverse transcription, HIV's single stranded RNA (ssRNA) is converted to double stranded DNA (dsDNA), allowing the genetic material to enter the nucleus where it becomes integrated into the host chromosomal DNA. The hijacked host cell produces long chains of HIV protein and RNA that are assembled into an immature, non-infectious form. Once pushed out of the cell, HIV protease breaks up the long protein chains to finally create the mature, infectious virion.

Currently approved HIV drugs fall into five categories: attachment inhibitors coreceptor antagonists, fusion inhibitors, reverse transcriptase inhibitors, integrase inhibitors and protease inhibitors.

## Attachment inhibitor coreceptor antagonists and fusion inhibitors

Drugs in these classes act by preventing HIV from entering host cells. Attachment inhibitor coreceptor antagonists block virus attachment to CD4+ T cells via a variety of mechanisms. Fostemsavir is a precursor of temsavir which acts by binding the HIV envelope glycoprotein gp120, while maraviroc binds to the host CCR5 receptor and acts as a negative allosteric modulator (2,3). In contrast, enfuvirtide is a fusion inhibitor that prevents fusion of the viral envelope with the CD4+ T cell membrane by blocking a required conformational change of the HIV1 complex (4).

# Reverse transcriptase inhibitors

More than half of currently approved antiretrovirals are reverse transcriptase inhibitors (RTIs) that work by blocking conversion of the virus's ssRNA into dsDNA, which is required for integration into the host's genomic DNA. There are two classes of RTIs: nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

NRTIs are prodrugs that require conversion to triphosphorylated derivatives before being incorporated in the proviral DNA. They act as chain terminators, blocking DNA synthesis due to a missing 3′ OH in the ribose ring. Tenofovir alafenamide (TAF), an acyclic analogue of deoxyadenosine 5′-monophosphate, is an example of a widely used NRTI that is included in most clinical guidelines for recommended first-line therapies (5).

NNRTIs are small hydrophobic compounds that inhibit DNA polymerisation by binding to an allosteric site near the enzyme's catalytic site. Efavirenz is an example of an NNRTI that was used for many years as a component of the first approved once-daily tablet regimen Atripla (6).

# Integrase inhibitors

Integrase inhibitors such as raltegravir work downstream of replication, blocking integration of the proviral DNA into the host chromosomal DNA. They work by binding to the catalytic domain of HIV-1 integrase, blocking the strand transfer reaction that prepares the proviral DNA for integration by lysing its processed 3′ ends (7).

# Protease inhibitors

Protease inhibitors act in the final stage of the HIV replication cycle - blocking cleavage of immature, precursor protein chains into mature protein components of the HIV virion, preventing it from becoming infectious. All current drugs of this class, except tipranavir, are peptidomimetics that interfere with HIV protease's active site. They contain a non-hydrolysable hydroxyethylene core that - unlike the peptide linkage of HIV's protein chains - cannot be cleaved (8). Ritanovir is an example of a peptidomimetic protease inhibitor that is widely used in combination therapies.

# Challenges to long term viral suppression

Combination therapies are effective at controlling HIV levels, but they are not a cure. Individuals must continue with a lifelong regimen of multiple drugs, which introduces a number of challenges. The first is maintaining long term adherence to the treatment regimen. Introduction of one-pill combination therapies like Atripla in the mid-2000s was a significantadvance, yet daily dosing protocols still make long term compliance difficult.

Treatment simplification helps and can take one of two forms: reducing the number of drugs required or reducing the dosing interval via long-acting or extended-release formulations. January 2021 marked the approval of Cabenuva™, which addresses both strategies. It is the first two-drug combination that can be used for maintenance therapy after achieving virological suppression, and is delivered as a once-monthly intramuscular injection (9). It is noteworthy that treatment simplification similarly helps with adherence to pre-exposure prophylaxis (PrEP) regimens. Daily PrEP formulations are highly effective at preventing HIV infection, but are challenging to adhere to and are often under used in vulnerable populations. The December 2021 approval of Apretude introduced the first injectable HIV PrEP treatment, which is given every two months. This extended-release injectable solution of cabotegravir (also an active component of Cabenuva™) has been shown to be as effective as standard PrEP regimens (10).

Jeopardised by drug toxicity, as well as by development and transmission of drug resistance. Tenofovir disoproxil fumarate (TDF) is well known for its harmful effects on kidneys and bones and thus has largely been replaced by a new form, tenofovir alafenamide (TAF), which provides less exposure (11). At the same time, integrase inhibitors are generally known to disturb aspects of metabolism, potentially resulting in weight gain and obesity (12).

Drug resistance - either acquired by infection with an existing drug-resistant strain or developed during treatment - is a serious concern. Long prescribed, early generation antiretrovirals with low genetic barriers of resistance have led to the emergence and transmission of drug-resistant HIV strains (13). Fortunately, newer generations of more potent retroviral agents with higher genetic barriers of resistance appear to be quite successful in treating these strains and in minimising the emergence of new resistant strains. Even so, with HIV's high mutation rate, the threat of newly emergent resistance remains.

## Research directions and status

Research is actively underway to discover, design and develop new therapies that meet as many as possible of four key characteristics: high potency, low toxicity, effectiveness against drug-resistant variants and amenability to long-acting formulations with longer dosing intervals. Current studies include work on compounds that act against existing targets and known mechanisms of actions, as well as discovery and development of compounds that act against as-yet-unexploited, or unknown targets and mechanisms of action.

# Novel antiretrovirals in advanced clinical trials

Two promising antiretroviral candidates are islatravir and lenacapavir (14). Currently in phase 3 development for HIV treatment, islatravir is being developed as a stand-alone agent and as part of a fixed-dose combination containing doravirine and islatravir (DOR/ISL). Similarly in phase 2/3 development for HIV treatment, lenacapavir is being developed as part of a fixed-dose combination of bictegravir and lenacapavir (BIC/LEN) and as an add-on agent to a failing regimen. Both are also in phase 3 development for HIV prevention.

Islatravir is an NRTI that undergoes conversion to a nucleotide analogue, which then becomes incorporated into the HIV DNA chain, resulting in chain termination (15). Unlike other NRTIs, islatravir acts through multiple mechanisms, including uniquely as a translocation inhibitor. Initial studies have suggested that islatravir is more potent than other NRTIs and performs well against multi-drug resistant HIV strains. With a long half-life, islatravir is a good candidate for long-acting formulations and has been shown to be well tolerated when delivered by a slow-releasing implant.

Lenacapavir is a member of a new capsid inhibitor class of antiretrovirals targeting the protein shell that protects HIV's genetic material and enzymes needed for replication. The capsid shell plays a role at multiple stages of the HIV replication cycle, providing multiple opportunities for interference. Lenacapavir acts early in the replication cycle by binding two contiguous capsid subunits, stabilising the capsid structure and preventing its disassembly (16). Like islatravir, lenacapavir appears to be a potent actor with a long half-life, making it a good candidate for long-acting formulations that may require as few as two doses per year.

# Additional targets and drug candidates in preclinical development

Although not as far advanced as islatravir and lenacapavir, many other drug candidates and targets are the subjects of active research and development, with a few having reached early-stage clinical trials. These include maturation inhibitors that interfere with late-stage protease cleavage, and broadly neutralising antibodies (bNAbs) that interfere with viral entry into the cell.

Today's preclinical research includes work on compounds that expand upon currently available antiretroviral drugs, with all five classes of antiretrovirals represented. It also encompasses studies that focus on hitherto unexploited druggable targets - including viral proteins, points of interaction between viral and host proteins, and even host factors.

# Concluding thoughts

Recent approvals and positive clinical trial results for long-acting maintenance therapies are the latest advancements in the 40+ year battle against HIV/AIDs. With time, we will be able to judge not just these drugs' effect on HIV treatment, but potentially their even greater impact on pre-exposure prophylaxis (PrEP) that helps to slow or stop the spread of HIV. In the future, thanks to ongoing clinical and preclinical research, we'll also be able to answer questions about whether new classes of agents can significantly impact prophylaxis and treatment, whether new targets can be exploited, and whether drug resistance can be contained while scientists bridge the gap to development of an antiretroviral free, functional cure. Perhaps most excitingly, we may be able to answer the question of whether other technologies, such as gene and cellular therapy, have the potential to clear reservoirs of latently infected cells or permanently silence the viral genome - providing a true cure for HIV/AIDs.

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