LONG-ACTING ANTIRETROVIRALS IN THE TREATMENT OF HIV-1

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Abstract

Although HIV has shifted from a death sentence to a manageable disease over the years, partly due to the development of highly efficacious antiretroviral therapies, its impact on the infected is lifelong. While there is currently a wide range of antiretroviral treatments available, the burden of HIV treatment remains high due to daily oral therapy. In the past decade, research into novel antiretrovirals for the treatment of HIV has slightly changed its course. Universities and pharmaceutical companies are now investigating and developing long-acting antiretroviral therapies. These long-acting antiretrovirals reduce the treatment burden by reducing the treatment frequency from once per day to once a week, once a month, or even once per six months. This search for novel compounds has resulted into two new treatment classes. With the first long-acting injectable antiretroviral treatment receiving market approval in 2020, the impact on the global HIV pandemic will manifest in the next couple of years. Long-acting antiretrovirals will decrease the treatment burden of the patient and likely increase treatment adherence, thus increasing the fraction of virologically suppressed HIV-patients. However, the cost of novel medication, an increased number of hospital visits for drug administration, and the mandatory oral lead-in period may result in a higher barrier of entry into the use of long-acting antiretrovirals by HIV-patients.

Introduction

Since its first reported cases in June 1981, the Human Immunodeficiency Virus (HIV) has grown to be a worldwide pandemic, which still claims about 680.000 lives per year to this day [1-3]. HIV is a lentivirus, which uses the CD4 protein on dendritic cells, macrophages, and CD4+ T-cells in combination with a chemokine receptor (most often CCR5 or CXCR5) to facilitate its entry into the cell (Figure 1). After its viral envelope fuses with the cell membrane, single stranded HIV RNA is turned into double stranded DNA by the enzyme reverse transcriptase (Figure 1) [4-6]. Subsequently, the newly formed double stranded DNA is integrated into transcriptionally active sites in the host's genome by the enzyme integrase [Figure 1] [4]. From that moment on, the virus will remain incorporated in the host cell's genome. The host cell will start producing new virus as soon as nuclear factors induce transcription in the locus where HIV was integrated. This new virus can then infect other cells in the host's body. If the infection is left untreated, the CD4+ population of cells will start to decrease, as HIV has various ways of accidentally killing its host cells [7]. If the CD4+ T-cell count falls below 200 cells/μL blood, the HIV infection progresses to a stage called acquired immunodeficiency syndrome (AIDS) [4]. Patients with AIDS have a much higher chance of developing opportunistic infections, as their immune system is much less functional [4, 6]. Historically, AIDS was seen as a death sentence, but with the development of increasingly efficacious antiretroviral (ARV) medication, HIV is manageable and has become a chronic disease.

The first ARV for HIV, zidovudine, a nucleoside-analogue inhibitor of the HIV reverse transcriptase enzyme, was brought to the market in 1987 [8, 9]. Since then, multiple ARVs in multiple drug classes have been developed to combat HIV. Combination ARV therapy uses multiple drugs with different mechanisms of action in the viral replication cycle. Currently, first-line treatment in treatment-naive patients often consists of two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and one drug, often an integrase strand transfer inhibitor (INSTI) such as dolutegravir, with a different mechanism of action [6, 8, 9]. HIV ARV treatments consist of pills, or solutions if the patient cannot swallow pills, which must be taken once or twice daily to achieve and maintain viral suppression [9, 10]. It is key to achieve and maintain viral suppression, as an uncontrolled HIV infection can develop into AIDS, and AIDS-related opportunistic infections may be deadly [10]. Additionally, the HIV reverse transcriptase enzyme is very error-prone and does not perform proof-reading [6]. These characteristics result in high replication and consequent mutation rates of HIV. If the patient has a non-suppressed HIV infection and sub-therapeutic exposures to ARVs, HIV may develop resistance against these ARVs and others in its drug class, which complicates treatment. However, due to the high pill burden, social stigma, and limited ARV availability in resource-limited settings, not all patients achieve viral suppression.

While traditional ARV regimens consist of daily oral pill intake, some pharmaceutical companies have spent the last years developing long-acting ARVs. These long-acting ARVs would, in most cases, eliminate the need for daily oral treatment and instead have periodical injections or other methods of drug delivery. Such a dosing regimen would promote treatment adherence and reduce the treatment load on the patient. There is currently one EMA-approved long-acting injectable treatment regimen, which consists of the integrase strand transfer inhibitor cabotegravir and non-nucleoside reverse transcriptase inhibitor rilpivirine [11].

Long-acting ARVs on the market or in development

Long-acting ARVs can belong to a multitude of different drug classes. Historically, the oral treatments have had a wide variety of mechanisms of action (Table 1, Figure 1).

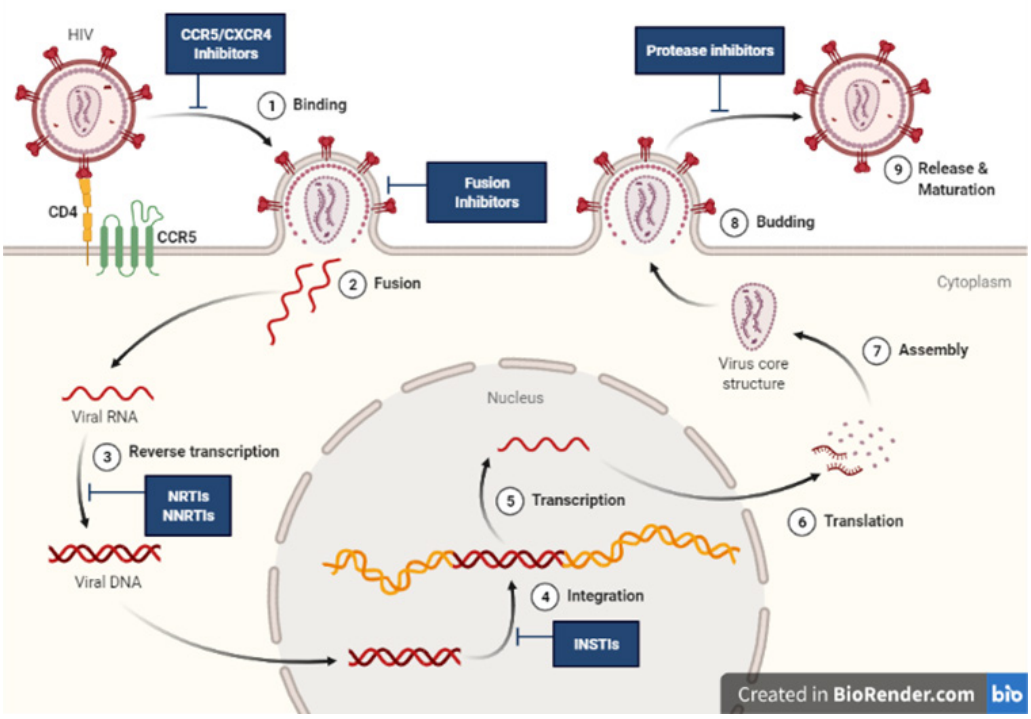

Figure 1: *Schematic overview of the HIV replication cycle. The replication cycle can be inhibited at several points. Successful HIV treatment makes use of a combination of at least two different modes of action (e.g., one drug inhibiting the reverse transcriptase/step 3 and another drug inhibiting the integrase/step 4). NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; INSTI: integrase strand transfer inhibitor. Reprinted from "HIV sites for Therapeutic Intervention", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates.*

Table 1: *Overview of drug classes currently in clinical use for the treatment of HIV-1. NRTI: Nucleoside Reverse Transcriptase Inhibitor; RT: Reverse Transcriptase; HIV: Human Immunodeficiency Virus; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; PI: Protease Inhibitor; INSTI: Integrase Strand Transfer Inhibitor; dsDNA: double-stranded DNA; CD4: Cluster of Differentiation 4; ARV: Antiretrovirals*

Drug class	**Mechanism of action (Figure 1)**	**Examples (not all are shown)**
NRTI	The HIV enzyme RT is necessary to turn single stranded HIV RNA into double stranded HIV DNA. NRTIs are nucleoside-analogues. As the RT-reaction is taking place, the NRTIs are built into the new DNA. However, NRTIs lack the 3'-OH group, which is necessary to keep building the new DNA strand. Incorporation of an NRTI-molecule leads to termination of the RT-reaction, and an incomplete or non-functional piece of HIV DNA. [9, 12]	Zidovudine/azidothymidine (1987) Lamivudine (1995) Abacavir (1998) Tenofovir disoproxil fumarate (2001) Emtricitabine (2003) Tenofovir alafenamide (2015)
NNRTI	NNRTIs also act on the RT enzyme, but with a different mode of action. The RT enzyme is structurally changed after an NNRTI binds in the NNRTI pocket. Although this does not fully stop the enzyme's activity, the change results in such a reduction of function that the NNRTIs are a highly effective class. [9, 12]	Nevirapine (1996) Efavirenz (1998) Etravirine (2008) Rilpivirine (2011) Doravirine (2018)
PI	The protease enzyme is needed to cleave immature HIV into its mature variant. PIs block the active site of protease and thus inhibit the formation of mature HIV and its subsequent release from the infected cell. [9, 13]	Saquinavir (1995) Ritonavir (1996) Atazanavir (2003) Tipranavir (2005) Darunavir (2006)

Fusion Inhibitors	Fusion inhibitors disrupt the process of viral entry into the cell by binding to the gp41 subunit of the envelope glycoprotein. As a result, a six-helix bundle, which brings together the viral and cellular membranes, cannot be formed, and the virus cannot enter the cell. [9, 14, 15]	Enfuvirtide (2003)
CCR5 Antagonists	CCR5 antagonists bind to the human chemokine receptor CCR5. CCR5 is one of the chemokine co-receptors that HIV can use to gain entry into the cell. By blocking the receptor, HIV cannot make use of this. However, other variants of HIV could make use of other chemokine receptors, such as CXCR5. [9, 15, 16]	Maraviroc (2007)
INSTI	INSTIs block the workings of the integrase enzyme. As a result, the newly formed HIV dsDNA will not be incorporated in the host's genome. [9, 17]	Raltegravir (2007) Dolutegravir (2013) Bictegravir (2018) Cabotegravir (2021)
Attachment Inhibitors	Attachment inhibitors prevent HIV from binding to CD4 by directly binding to the viral envelope gp120. This appears to be the earliest step in which HIV can be combatted medicinally, apart from neutralising antibodies. [9, 15, 18]	Fostemsavir (2020)
Post-Attachment Inhibitors	Post-attachment inhibitors bind to CD4. Although binding of HIV to CD4 is not prevented, post-attachment inhibitors prevent the subsequent co-binding to chemokine receptors, preventing HIV entry into the cell. CD4 retains its immunological function when post-attachment inhibitors are used. [9, 15]	Ibalizumab (2018) Note: Ibalizumab (and most other drugs in this class) must be administered intravenously and cannot be taken orally.
Pharmacokinetic Enhancers	Pharmacokinetic enhancers generally alter liver enzyme activity, which would normally metabolise other ARVs. This way, the same dose of ARV can lead to a higher or longer exposure to the drug, resulting in higher efficacy but also risking toxicity as a result of overexposure. [9]	Cobicistat (2014)

Current oral HIV treatment has been efficacious for treatment-adherent patients. However, some patients are unable to swallow pills, struggle with treatment adherence, or have an altered absorption state, rendering the standard oral treatment ineffective for them. Logically, pharmaceutical companies have turned to ARVs that are already in use for the treatment of HIV to create long-acting treatment variants (Table 2). However, some drug classes have more suitable characteristics to be used as a long-acting treatment for HIV, such as a favourable resistance profile or a longer elimination half-life. Due to the large number of antibodies that are in development against HIV, these are not described in more detail in this article [19]. The search for suitable compounds for long-acting treatment has also yielded some novel drug classes, such as nucleoside reverse transcriptase translocation inhibitors and capsid inhibitors [20].

These long-acting ARVs offer various treatment options for both treatment-naive patients as well as patients that seem to have exhausted most other ARV options. While most long-acting ARVs have not set a definitive optimal dosing regimen, all long-acting therapy will relieve (some) pill burden off the patient. The dosing intervals are tested as short as one week (islatravir), one to two months (Cabenuva), to six months (lenacapavir). While this increased dosing interval eases the patient's treatment burden, the hospitals will have an increased workload, as patients must visit the hospital for injections and implants. However, a lot can change before regulatory approval, and, with more study time and possibly the use of pharmacokinetic enhancers, the dosing interval can perhaps be prolonged further for some of the long-acting ARVs.

Table 2: *Long-acting treatments currently in development. Neutralising antibodies clustered, as a multitude of companies are investigating several antibodies in different stages of clinical development. IV: Intravenous; INSTI: Integrase Strand Transfer Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; IM: Intramuscular; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NRTTI: Nucleoside Reverse Transcriptase Translocation Inhibitor; PrEP: Pre-Exposure Prophylaxis; PI: Protease Inhibitor; SC: subcutaneous; TAF: Tenofovir alafenamide; IP: Intraperitoneal.*

Compound name(s)	Drug class	Formulation	Clinical development phase and dosing frequency
Albuvirtide	Fusion inhibitor	IV infusion	Phase III (TALENT; NCT02369965): Once per week
Atazanavir	PI	Injectable (SC, IM)	Preclinical
Cabenuva (Cabotegravir + Rilpivirine)	INSTI + NNRTI	Injectable (IM)	On market: Once per 1-2 months
Combinectin	Entry inhibitor	Injectable (SC)	Phase I (NCT03984812): Once per week
Elsulfavirine	NNRTI	Oral; Injectable (SC, IM)	Phase Ib (NCT03730311): Once per week; Preclinical
GS-CA1	Capsid inhibitor	Injectable (SC)	Preclinical
GSK'937	Maturation inhibitor	Injectable (SC, IM)	Preclinical
Islatravir (EFdA)	NRTTI	Oral; Subdermal implant (PrEP)	Phase III (Impower-024; NCT04652700): Once per month; Phase I
Lenacapavir	Capsid inhibitor	Injectable (SC), oral	Phase III (CAPELLA; NCT04150068): Once per 6 months
Raltegravir	INSTI	Injectable (SC)	Preclinical
Ritonavir	PI	Injectable (SC, IM)	Preclinical
TAF	NRTI	Subdermal implant	Phase I/II (CAPRISA 018): Once per 6 months
Various neutralising antibodies	HIV-1 envelope protein antibodies	Injectable (IV, IP)	Various stages of development

The long-acting ARVs are not only being tested as treatment. Some of the compounds may hold the potential to exhibit a protective function against an HIV infection as well [21, 22]. In such a case, the drug must be taken before participating in activities that put the individual at risk of an HIV infection, in a treatment method called pre-exposure prophylaxis (PrEP) [21, 22]. Such PrEP treatments are already available as daily oral pills – most commonly in the form of tenofovir disoproxil fumarate paired with emtricitabine, or both combined in a non-generic fixed dose tablet– but these exhibit a large pill burden on the individual. In order to remain safe, the treatment must be taken each day during high-risk behaviour periods, such as sexual activity in men who have sex with men. Reducing the burden of treatment adherence by replacing daily oral PrEP with any of the long(er)-acting ARVs can offer easier, more reliable protection to those frequently at risk of an HIV infection [21, 22].

Discussion

As the pathology of HIV is understood better over the years, a much more targeted approach can be taken to combat HIV. The global effort to combat the novel viral infection in the eighties resulted in the repurposing and regulatory approval of a drug within a couple of years after the discovery of HIV. What followed was twenty years in which therapies to treat HIV in new ways were presented on the market every year or two. Now that basic, effective treatment has been established, the next generation of anti-HIV medication can focus on other aspects of the disease, such as reducing possible side effects of the medication, reducing the pill burden, and effective prevention of HIV infection.

The upcoming long-acting ARVs offer current patients a reduction in their daily disease burden or new treatment options if other options have been exhausted.

However, there are limitations to the long-acting ARVs. Although the daily burden of the disease is decreased, the importance of treatment adherence is increased. Missing injections or pills will result in a subtherapeutic concentration of the ARV, allowing

for a viral rebound in the blood HIV RNA count. This may, in turn, lead to novel mutations in HIV and result in treatment resistance, rendering the long-acting ARV and possibly other (oral) drugs in the same drug class useless for this patient. In the same manner, stopping the treatment and switching to a different treatment regimen is not without risk of developing treatment resistance, as the currently approved regimen of cabotegravir and rilpivirine can be detected in blood up to a year after the last injection.

Next to this, there are some problems related to care organisation. If patients start using the long-acting injectable ARVs, these must be administered in the hospital or clinic which will result in additional work for the hospital or clinic. This would also require the hospital or clinic to train additional staff to administer these injectables. The injectables must remain cooled from production until the moment of administration in the patient. Together, these points limit the impact long-acting injectable ARVs could have in resource-limited settings.

Another limiting aspect comes in the form of the oral lead-in period for the injectables. This oral lead-in period is used to test for hypersensitivity and other adverse events related to treatment in the patient. As the long-acting ARV injectables will release their active substance for a long time, the patient could face long persisting negative effects of the medication if they are hypersensitive. The oral lead-in period raises the barrier of entry into long-acting ARV injectables, as not all patients may be willing to put in the work to closely monitor their health for up to a month or may be unable/unwilling to swallow new pills for a month. However, there is no consensus on the use of the oral lead-in period. Following an update to the summary of product characteristics, this lead-in period is now optional for the cabotegravir and rilpivirine combination injectable treatment. It is not yet clear how other treatments will tackle this problem.

As these long-acting treatments are new, there has not yet been ample time to build clinical knowledge regarding special patient populations, such as children or pregnant women, and interactions with other drugs. Safety data regarding pregnancy and children are more difficult to gather and will take a long time, as low concentrations of the long-acting treatments will remain present in the body for a long time, even after discontinuation of treatment. Next to this, the clinical application of long-acting treatments may be limited by the nature of HIV treatment. It is difficult to find partner drugs for long-acting treatments. These partner drugs must be of a different drug class and preferably be dosable in the same interval. Combine this with patient-specific resistance or side effects, and the development of new long-acting treatment regimens is now a lot more difficult.

The final limitation of long-acting ARVs comes at its price. Currently, only one option is on the market to be used as a full treatment regimen. Disregarding the price of the oral lead-in period of 28 days and the increased first injected dose, maintenance doses will cost $1,036, - (€895.22) per month and are likely not covered by insurance. For reference, a commonly prescribed oral combination pill of non-generic doravirine, lamivudine, and tenofovir disoproxil fumarate will cost €530.40 per month, which is covered by insurance in The Netherlands. While long-acting ARVs seem to be the way forward for HIV treatment and prevention, time will tell if these are the way forward for HIV patients.

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