

## Review Article



# An Overview of Human Immunodeficiency Virus-1 Antiretroviral Drugs: General Principles and Current Status

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### Conflict of Interest

No conflicts of interest.

## ABSTRACT

Treatment with highly active antiretroviral therapy (HAART) can prolong a patient's life-span by disrupting pivotal steps in the replication cycle of the human immunodeficiency virus-1 (HIV-1). However, drug resistance is emerging as a major problem worldwide due to the prolonged period of treatment undergone by HIV-1 patients. Since the approval of zidovudine in 1987, over thirty antiretroviral drugs have been categorized into the following six distinct classes based on their biological function and resistance profiles: (1) nucleoside analog reverse-transcriptase inhibitors; (2) non-nucleoside reverse transcriptase inhibitors; (3) integrase strand transferase inhibitors; (4) protease inhibitors; (5) fusion inhibitors; and (6) co-receptor antagonists. Additionally, several antiretroviral drugs have been developed recently, such as a long active drug, humanized antibody and pro-drug metabolized into an active form in the patient's body. Although plenty of antiretroviral drugs are beneficially used to treat patients with HIV-1, the ongoing efforts to develop antiretroviral drugs have overcome the drug resistances, adverse effects, and limited adherence of drugs observed in previous drugs to some extent. Furthermore, studies focused on agents targeting latent HIV-1 reservoirs should be strengthened, as that may lead to eradication of HIV-1.

**Keywords:** Human immunodeficiency virus; Anti-HIV-1 drugs; HIV-1 Tat

## INTRODUCTION

In 1981, the United States Centers for Disease Control and Prevention (US CDC) reported the seemingly sudden development of a fatal infectious disease among homosexuals and drug users. This new disease caused a deficiency in the patient's immune state, leading to Kaposi sarcoma, *Pneumocystis jirovecii* pneumonia, lymphoma and, eventually, death. Because the disease was initially detected mainly in male homosexuals, it was initially called "Gay Related Immunodeficiency Syndrome" (GRID). In 1983, Luc Montagnier and other members of the INSTITUT PASTEUR, France, isolated a retrovirus from the lymph node of a lymphoma patient, which was later identified as a virus called human immunodeficiency virus-1 (HIV-1) [1-4]. Thereafter, the life cycle of the virus was discovered through many studies, thus enabling

**Author Contributions**

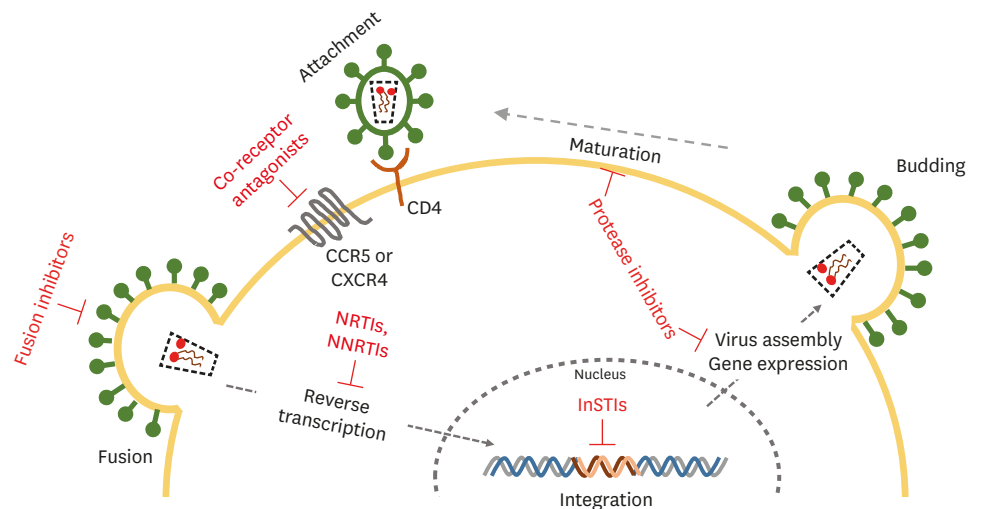
Conceptualization: CHY. Data curation: CHY, YHS, CMP. Formal analysis: CMP. Funding acquisition: CHY. Project administration: CHY. Supervision: CHY. Visualization: CMP. Writing - original draft: CHY, YHS, CMP. Writing - review & editing: CHY.

the rapid development of therapeutic agents and diagnostic technology. Because the main characteristic of HIV-1 is the reverse transcription process, a therapeutic drug development strategy aimed at blocking this process was applied first of all, and the first HIV-1 treatment drug, zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor, was developed in 1987 [5]. This was followed by the successive development of a non-nucleoside reverse transcriptase inhibitors, protease inhibitors, viral entry inhibitors, and virus integrase strand transferase inhibitors. More recently, continuous progress has been made in improving the effects of existing drugs as well as in developing a new paradigm of HIV-1 drugs. This study aims to review the process of development of these drugs and their mechanisms, along with more recently developed antiviral agents, in order to suggest a developmental direction for HIV/acquired immune deficiency syndrome (AIDS) therapeutic drugs.

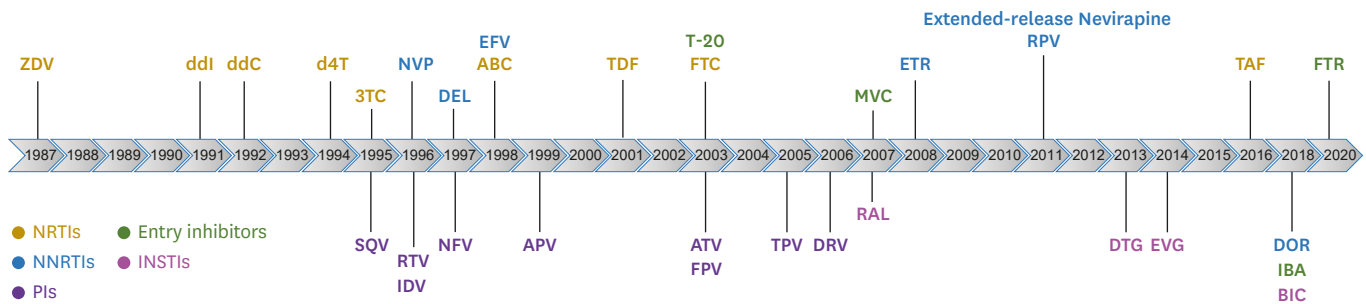
**THE HIV-1 REPLICATION STEPS AS THE DRUG TARGET**

Since the discovery of HIV-1 in 1983, the life cycle of HIV-1 has been revealed and therapeutic drugs that inhibit HIV-1 proliferation have been developed on the basis of the results of studies [6]. HIV-1 binds to the receptor CD4 of CD4<sup>+</sup> T cells and co-receptors (CCR5 or CXCR4), and then enters the host cell [7]. After entry, the viral RNA genome is transcribed to DNA by reverse transcriptase, moved to the nucleus, and then integrated into a host chromosome by integrase. The inserted viral DNA (provirus), with the help of the viral transcription factor Tat (Trans-activator of Transcription) and several factors in the host cell, expresses viral mRNA. The full length of the expressed viral mRNA becomes the genome of the progeny virus, and some mRNAs are translated into several proteins necessary for outer membrane proteins (gp120 and gp41) and formation of a virion, which then enclose the host cell membrane and are released out of the cell. At this time, the virion is matured by viral protease and transformed into a virus with infectivity, which then re-infects the nearby cells so as to begin a new viral life cycle (Fig. 1) [8].

From the appearance of the first reverse transcriptase inhibitor, ZDV, in 1987 to the recent integrase strand transferase inhibitor, bicitgravir (BIC), about thirty HIV-1 therapeutic



**Figure 1.** Stages of the HIV-1 life cycle and current target for antiretroviral drugs. HIV-1, human immunodeficiency virus-1; NRTIs, nucleoside analogue reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; InSTIs, integrase strand transferase inhibitors.



**Figure 2.** Timeline for FDA-approved antiretroviral drugs.

FDA, food and drug administration; ZDV, zidovudine; ddI, didanosine; ddC, zalcitabine; d4T, stavudine; 3TC, lamivudine; SQV, saquinavir; NVP, nevirapine; RTV, ritonavir; IDV, indinavir; DEL, delavirdine; NFV, nelfinavir; EFV, efavirenz; ABC, abacavir; APV, asunaprevir; TDF, tenofovir disoproxil fumarate; T-20, enfuvirtide; FTC, emtricitabine; ATV, atazanavir; FPV, fosamprenavir; TPV, tipranavir; DRV, darunavir; MVC, maraviroc; RAL, raltegravir; ETR, etravirine; RPV, rilpivirine; DTG, dolutegravir; EVG, elvitegravir; TAF, tenofovir alafenamide; DOR, doravirine; IBA, ibalizumab; BIC, bictegravir; ; FTR, fostemsavir; NRTIs, nucleoside reverse-transcriptase inhibitors; NNRTIs, non-nucleoside reverse-transcriptase inhibitors; INSTIs, integrase strand transfer inhibitors; PIs, protease inhibitors.

drugs capable of inhibiting each stage have been developed and used in the treatment of HIV-1 patients (Fig. 2) [8, 9]. These HIV-1 therapeutic drugs have been classified into five types according to their targeted stage and chemical forms: reverse transcriptase inhibitors (nucleoside type and non-nucleoside type), protease inhibitors, integrase strand transferase inhibitors, CCR5 antagonists, and membrane fusion inhibitors [8-10].

## REVERSE TRANSCRIPTASE INHIBITORS

Since the development of the first HIV-1 therapeutic drug, namely the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine (3'-azido 3'- deoxythymidine, ZDV), in 1987, various nucleoside reverse transcriptase inhibitors have been developed one after another [6, 11]. As resistance to nucleoside-like drugs gradually increased, the non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine (NVP), was developed first in 1996, followed by the development of several NNRTIs [12].

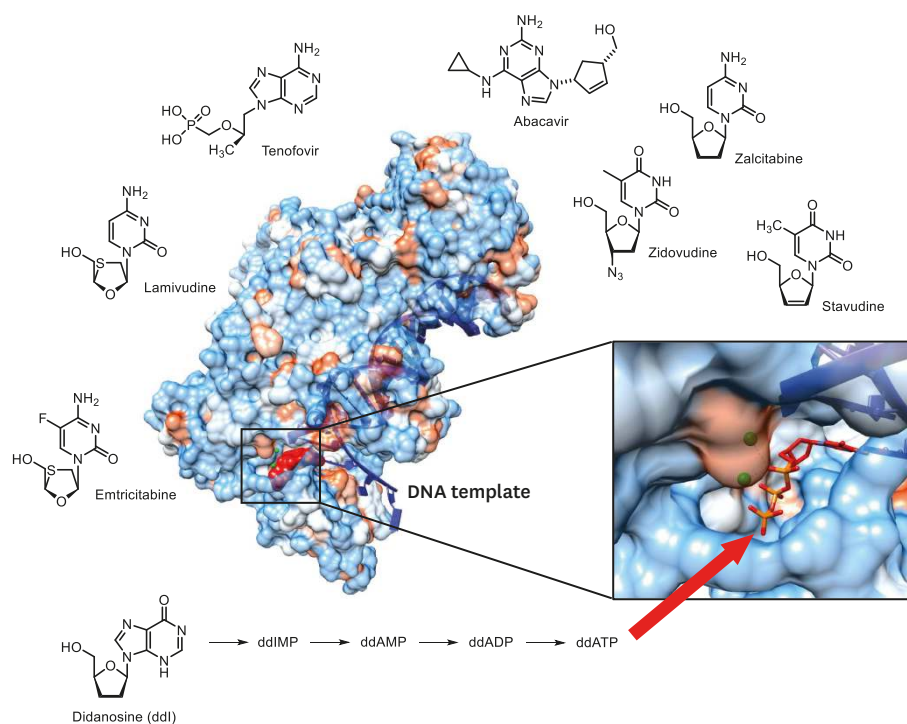
### 1. Nucleoside reverse-transcriptase inhibitors (NRTIs)

NRTIs constitute a group of anti-HIV-1 drugs that were approved for the first time by the US food and drug administration (FDA). These drugs are mainly administered as precursors, which then enter the host cell and are phosphorylated to the nucleotide form in order to display activity as a drug [13, 14]. So far, eight types of NRTIs have been developed; recently, tenofovir alafenamide (TAF), with improved pharmacological activity of tenofovir, was developed and used (Table 1) [15]. These drugs commonly lack a 3-OH (hydroxyl group) on

**Table 1.** Nucleos(t)ide reverse-transcriptase inhibitors

Generic name	Brand name	FDA approval date
Zidovudine	Retrovir	1987
Didanosine	Videx	1991
zalcitabine	Hivid	1992
Stavudine	Zerit	1994
Lamivudine	Epivir	1995
Abacavir	Ziagen	1998
Tenofovir disoproxil fumarate	Viread	2001
Emtricitabine	Emtriva	2003
Tenofovir alafenamide fumarate	Vemlidy	2016

FDA, food and drug administration.



**Figure 3.** X-ray crystal structure of HIV-1 RT in complex with viral DNA template/primer and Nucleos(t)ide reverse-transcriptase inhibitors. A nucleoside inhibitor didanosine (ddl) is converted to ddAMP missing OH, following termination of DNA synthesis by the incoming dTTP. The cartoon of the crystal structure has been adapted from data deposited by Huang et al. (1998) [87].

RT, reverse-transcriptase; HIV-1, human immunodeficiency virus-1; DNA, deoxyribonucleic acid; ddAMP, 2'-5'-Dideoxyadenosine-5'-monophosphate; dTTP, deoxythymidine triphosphate; OH, hydroxyl group.

the deoxyribose moiety of the nucleoside, and thus demonstrate an action mechanism during viral DNA synthesis, which terminates viral DNA synthesis, by incorporating themselves into the growing DNA chain and blocking the 3'-5' phosphodiester bond with the next incoming nucleotide (Fig. 3) [10, 16].

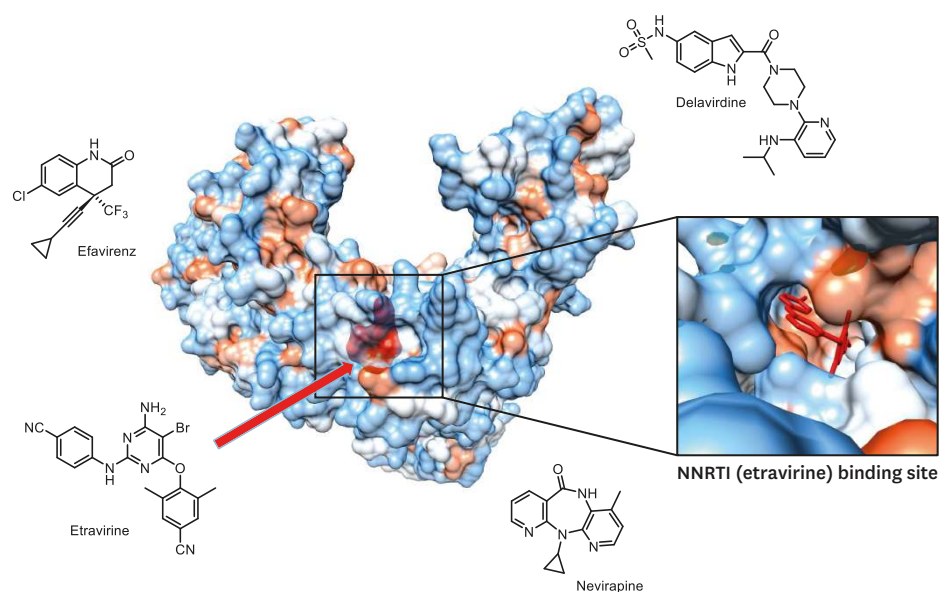
## 2. Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)

NNRTIs, unlike NRTIs, do not act as a terminator for viral DNA synthesis, but directly bind to the hydrophobic pocket near the active site of the reverse transcriptase to change the enzyme structure so as to inhibit enzymatic action (Fig. 4) [10, 16]. As such, they show no cross-resistance with existing NRTIs. Although these high potent NNRTIs were still under development recently, the single administration of these drugs makes HIV-1 vulnerable to the acquisition of resistance and develops cross-resistance to other NNRTIs. Therefore, these drugs are administered in combination with other anti-HIV-1 drugs. So far, seven types of these drugs have been approved (Table 2).

**Table 2.** Non-nucleoside reverse-transcriptase inhibitors

Generic name	Brand name	FDA approval date
Nevirapine	Viramune	1996
Delavirdine	Rescriptor	1997
Efavirenz	Sustiva	1998
Etravirine	Intelence	2008
Extended-release Nevirapine	Viramune XR	2011
Rilpivirine	Edurant	2011
Doravirine	Pifeltro	2018

FDA, food and drug administration.



**Figure 4.** Crystal structure of HIV-1 RT complexed with etravirine and Non-nucleoside reverse-transcriptase inhibitors. The cartoon of the crystal structure has been adapted from data deposited by Lansdon et al. (2010) [88]. HIV-1, human immunodeficiency virus-1; RT, reverse-transcriptase.

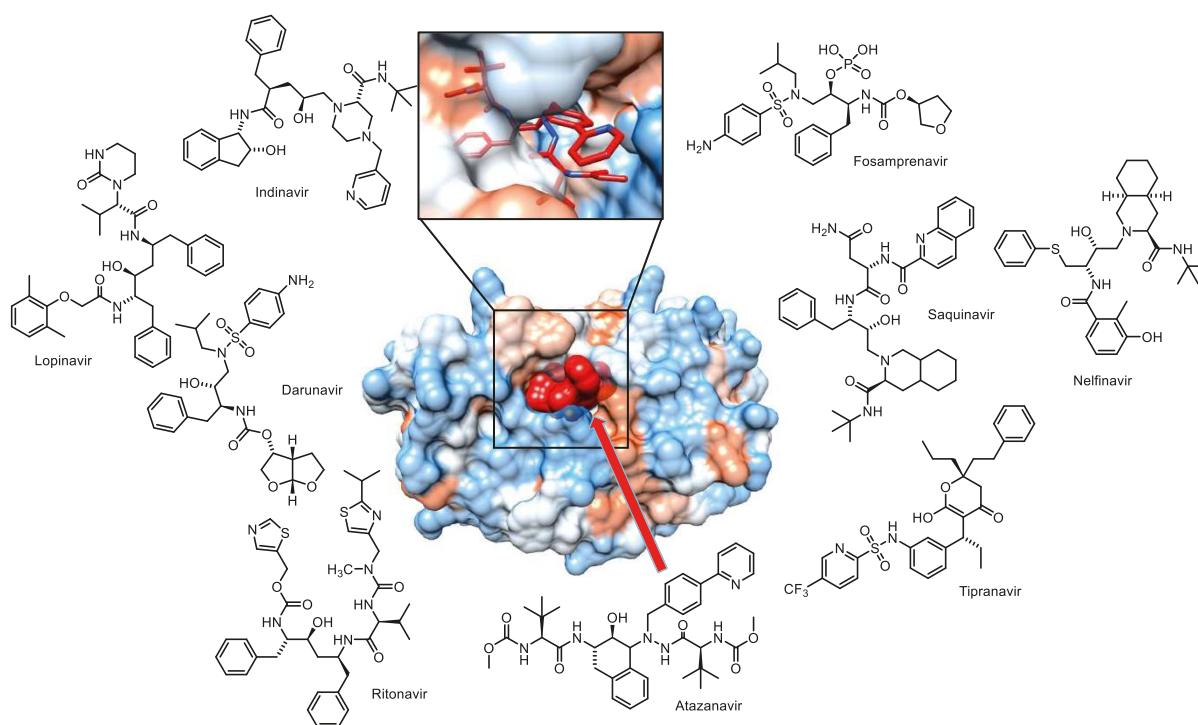
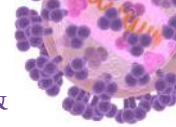
## PROTEASE INHIBITORS (PIs)

After the mid-1990s, various protease inhibitors (PIs) against HIV-1 were developed (Table 3) [17, 18]. HIV-1's protease is an important enzyme that cuts the precursor proteins of GAG (group-specific antigen) and GAG-POL (polymerase) contained in the virion without infectivity and turns them into a matured virus with infectivity [19]. Therefore, protease inhibitors were welcomed with great expectations in the area of novel anti-HIV-1 drugs. During the earlier period, when such protease inhibitors were being developed, they were thought less likely to develop resistance because this enzyme plays a very important role in viral proliferation and is as tiny as 11 kDa [20]. But resistant mutation in patients with PI treatment was observed to develop with very high frequency, and it was found to be vulnerable to cross-resistance - particularly because all PIs have similar chemical structures for binding to the active site of the enzyme [20, 21]. Thus, PIs are mainly used in 'cocktail therapy' with three types of anti-HIV-1 drugs at present [10]. Also, the long-term use of PIs results in the development of disadvantages such as a change of lipid distribution in the body and abnormal lipid metabolism [22]. Thus, no new PIs have been developed since darunavir in 2006 (Fig. 5) [10].

**Table 3.** Protease inhibitors

Generic name	Brand name	FDA approval date
Saquinavir	Invirase	1995
Ritonavir	Norvir	1996
Indinavir	Crixivan	1996
Nelfinavi	Viracept	1997
Amprenavir	Agenerase	1999
Atazanavir	Reyataz	2003
Fosamprenavir	Lexiva	2003
Tipranavir	Aptivus	2005
Darunavir	Prezista	2006

FDA, food and drug administration.



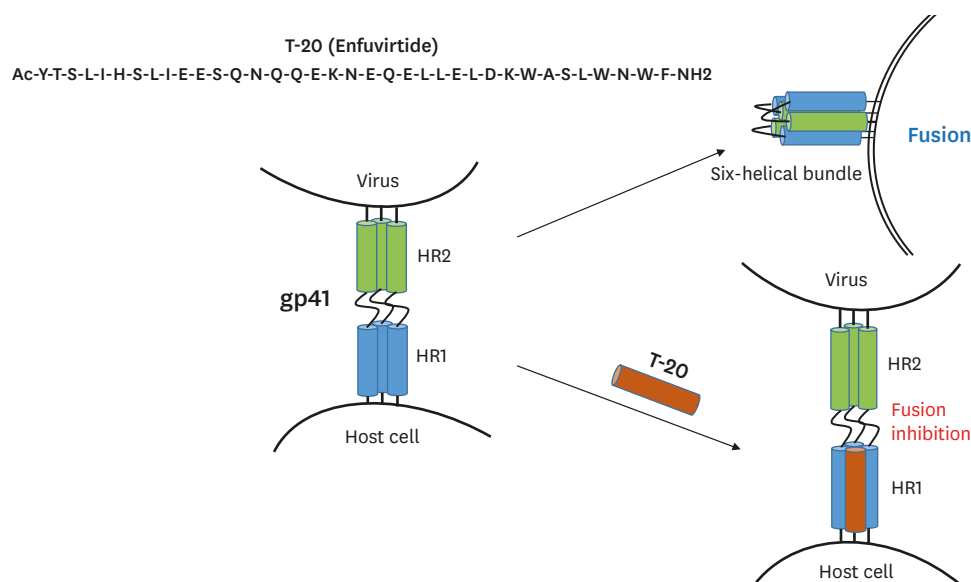
**Figure 5.** The crystal structure of HIV-1 protease blocked by atazanavir and protease inhibitors. The cartoon of the crystal structure has been adapted from data by King et al. (2012) [89]. HIV-1, human immunodeficiency virus-1.

## MEMBRANE FUSION INHIBITORS

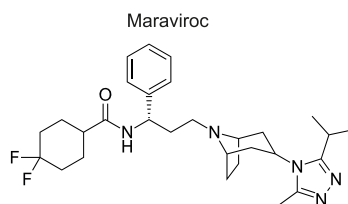
In 1997, a study on crystal structure revealed that glycoprotein 41 (gp41) for viral fusion consisted of two helical repeats, namely, heptad repeat 1 (HR1) and heptad repeat 2 (HR2), which interact with each other to form a six-helix bundle structure from trimeric gp41, after which the viral membrane fuses with the cell membrane; thus, a peptide capable of blocking this process was developed (Fig. 6) [23, 24]. Then, it was approved by the US FDA in 2003 as enfuvirtide (T-20, Fuzeon), which has mainly been prescribed as an injection therapy for patients who show multi-drug resistance and/or adverse effects during treatment with existing drugs [25-27].

## CCR5 ANTAGONISTS

Maraviroc (MVC) is an antagonist of the HIV-1 co-receptor CCR5 and a small-molecule drug developed in 2007 (Fig. 7) [28]. It binds to the hydrophobic pocket of the CCR5 co-receptor and changes its conformation, and interrupts the binding of the V3 loop of the viral membrane protein gp120 to CCR5, in order to prevent viral entry into the host cell [29]. Although this drug targets the co-receptor of the host cell, it has been reported to acquire resistance using a different resistance mechanism, unlike other anti-HIV drugs that directly bind to the viral protein [30, 31]. The mechanisms of resistance acquisition for this drug include a change of the infection route to CXCR4 instead of CCR5 of the viral protein gp120, a strengthening of coherence with CCR5 stronger than maraviroc, and the acquisition of penetration ability by recognizing the maraviroc-CCR5 complex [10, 32, 33].



**Figure 6.** Peptide sequences of T-20 and the mode of action of T-20. The formation of the gp41 six alpha-helix bundle is blocked by T-20 (enfuvirtide) in the final step of the HIV-1 entry process. The cartoon has been adapted from data by Berkhout et al. (2012) [90]. HIV-1, human immunodeficiency virus-1.



**Figure 7.** Chemical structure of the CCR5 Antagonist (Maraviroc) [91].

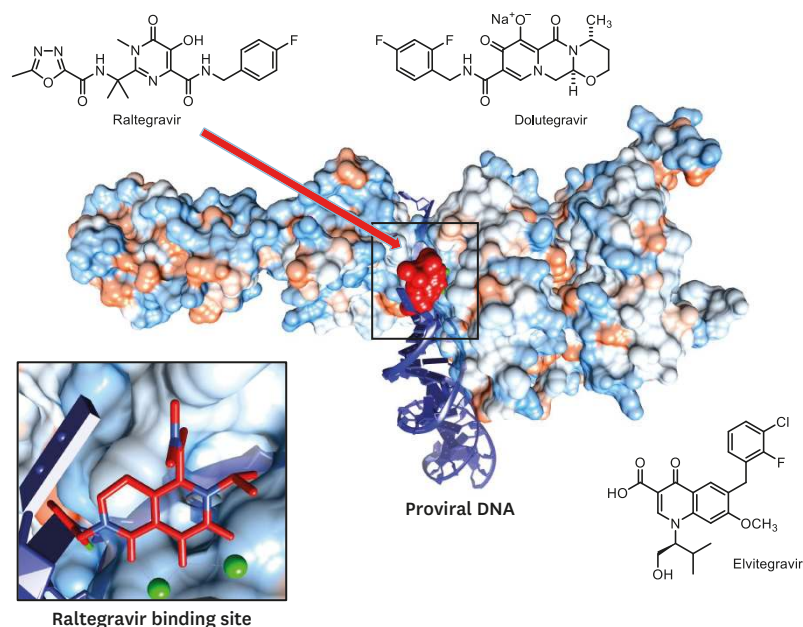
## INTEGRASE STRAND TRANSFERASE INHIBITORS (InSTIs)

After reverse transcription is terminated, viral DNA is incorporated into the host chromosome to become a provirus. From then on, the virus can express its own genes and produce its progeny [34, 35]. As such, integrase is necessary for incorporation of the viral DNA into the host chromosome, which is responsible for the essential stages of the viral life cycle. This integrase is the target of the most recently developed anti-HIV-1 drugs [34, 35]. The integrase performs the following action: it cuts off the 3'-OH group and then transfers the viral strand into the host chromosome for integration [36, 37]. Integrase inhibitors - called integrase (DNA) strand transferase inhibitors (InSTIs) - have been developed to target the function of viral strand transfer among them. Raltegravir (RAL) was first developed as an integrase inhibitor in 2007, followed by dolutegravir (DTG) in 2013 and elvitegravir (EVG) in 2014 (Table 4) [38-40]. These drugs bind to two magnesium ions required for binding the

**Table 4.** Integrase strand transfer

Generic name	Brand name	FDA approval date
Raltegravir	Isentress	2007
Dolutegravir	Tivicay	2013
Elvitegravir	Vitekta	2014
Bictegravir	Biktarvy (BIC/FTC/TAF)	2018

FDA, food and drug administration; BIC, bictegravir; FTC, emtricitabine; TAF, tenofovir alafenamide.



**Figure 8.** The crystal structure of virus integrase complexed with raltegravir [41] and integrase strand transfer inhibitors.

active site of integrase and the viral DNA, and thus block the binding of the integrase active site and the DNA (Fig. 8) [10, 41-43]. After the phase 3 clinical trial, BIC was approved by the US FDA in 2018 in the form of a triple complex BIC/emtricitabine (FTC)/TAF with 2 types of reverse transcriptase inhibitors [44]. During a clinical study, this triple complex showed inhibitory effects on virus proliferation similar to those of the triple complex DTG/FTC/TAF including DTG, and also showed fewer adverse drug effects [45, 46]. Furthermore, BIC develops less resistance and is highly effective against the resistance mutation observed in DTG. Its half-life is 18 hours [47-49].

## PHARMACOKINETIC BOOSTER

Several years ago, cobicistat (COBI) without its own antiviral properties was developed as a booster, which can increase the plasma concentration and absorption rate of antiretroviral agents [50-53]. Approved by the US FDA in August 2012, COBI, a potent inhibitor of the cytochrome P450 3A enzyme, inhibits intestinal transport proteins following an increase of the overall absorption of several antiretroviral agents (atazanavir, darunavir and tenofovir) [54]. Otherwise, it increases the efficacy of the integrase strand transferase inhibitor (InSTI) by inhibiting liver enzymes hydrolyzing the InSTI [55, 56].

## RECENT PROGRESS OF NEW ANTIRETROVIRAL DRUGS

### 1. Long-term active drugs: Cabotegravir (CAB) + Rilpivirine (RPV)

Antiviral agents that act for a long time in the patient's body have been developed as long-term active drugs, such as cabotegravir and rilpivirine [57]. The half-life of cabotegravir (CAB, GSK744), an InSTI currently under development, lasts for up to forty days, while that of nanoparticle-type nano-suspension generally lasts for 21 - 50 days, but can last for up to 90 days,



and just 1 dosage can effectively inhibit viral proliferation [58, 59]. Meanwhile, rilpivirine (RPV) is an already developed NNTRI. The half-life of a 25 mg tablet of rilpivirine is up to 50 days, while the half-life of long-term active nano-suspension may be as much as 90 days [12, 60]. According to the results of a recent randomized phase 2b clinical trial, the combined administration of these two drugs maintained the virus concentration in the blood at below 50 copies/mL in 94% of patients taking the drugs at up to 8-week (56 days) intervals, and increased the convenience of patients compared to drugs who were administered them on a daily basis [61]. After a phase 3 clinical trial study, the two-drug regimen was submitted to the US and the EU for approval in 2019. It is expected that the development of long-term active drugs will greatly increase the quality of life for patients who can take drugs once every few months [62-64]. Otherwise, the injectable long-acting CAB is being investigated for pre-exposure prophylaxis (PrEP) in HIV-uninfected men under HPTN083 (HIP Prevention Trials Network 083) as of 2020.

## 2. Doravirine (DOR)

DOR is a next-generation NNRTI approved by the US FDA in August 2018 for the treatment of multi-drug-resistant HIV-1 in a combination tablet, DOR/3TC/TDF (Delstrigo) [65]. It seldom demonstrates a drug-drug interaction when combined with other anti-HIV-1 drugs, and shows a decreased level of LDL compared to other anti-HIV-1 drug groups, while its central nervous system (CNS) side effects are almost non-existent [66, 67]. Considerable attention is being paid to the FDA approval depending on the results of a supplementary study [68, 69].

## 3. Fostemsavir (FTR)

FTR is metabolized to temsavir (TMR) in the body and binds to gp120 of the virus, and then inhibits the penetration of HIV-1 into the host cell by blocking binding with the co-receptors CCR5 and CXCR4 [70, 71]. Cross-resistance with other types of antiretroviral drugs has not yet been reported [70-73]. FTR was approved by the US FDA in July 2020 for the treatment of multi-drug-resistant HIV-1.

## 4. Ibalizumab (IBA)

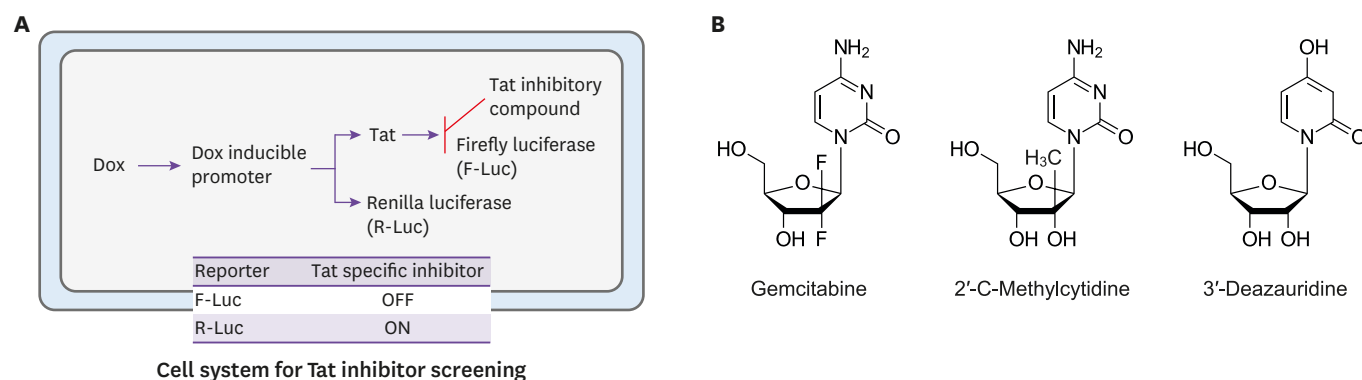
IBA is a humanized immunoglobulin G4 monoclonal antibody that binds to CD4 of the host cell with high affinity [74, 75]. It effectively inhibits the entry of HIV-1 by using the co-receptor CCR5 or CXCR4, into the host cell. In addition, it shows a therapeutic effect in existing multi-drug resistant viruses [74]. It was approved by the US FDA in March 2018 for the treatment of multi-drug-resistant HIV-1, and is used as an intravenous injection every 14 days [76, 77]. It has been recommended for possible combination therapy with other anti-retroviral drugs such as InSTI, PI and NRTI/NNRTI, all of which have a mode of action distinct from that of IBA [77, 78].

## 5. Islatravir

Islatravir is being developed as a nucleoside reverse transcriptase translocation inhibitor for HIV-1 prevention and has multiple mechanisms of action [79]. Islatravir is notable for its high potency and long plasma half-life (~120 hours), and has a 4-fold lower IC50 than any other NRTIs and a greater inhibitory effect against NRTI mutations, including M184I/V, K65R and K70E. It is being tested in its phase 3 of development as an HIV-1 treatment and PrEP using a two-drug fixed dose combination of DOR and islatravir [80].

## 6. GS-6207

GS-6207 is a small molecule that inhibits the HIV-1 capsid protein. It binds tightly at a conserved interface between capsid protein monomers, causing interference in the interaction between the capsid protein and cellular cofactors such as Nup153 and CPSF6,



**Figure 9.** Schematic diagram of discovery of the HIV-1 transcriptional inhibitor (A) and nucleoside analogues of novel HIV-1 transcription-repressing compounds (B) [86]. HIV-1, human immunodeficiency virus-1; DOX, doxycycline; Tat, viral transactivator; OFF, signal-off; ON, signal-on.

which are essential for multiple phases of the viral replication cycle. In Phase 1 clinical studies, monotherapy with a subcutaneous dose of GS-6207 (450mg) exhibited a mean 2.2 log reduction of the viral load at day 10, and showed sustained anti-viral active concentrations for more than 6 months. Due to the potency of GS-6207, the agent has been proposed as a potent long-acting drug to treat or prevent infection with HIV-1 [81, 82].

### 7. Viral transcription factor Tat as therapeutic target

To overcome the resistance to HIV-1 drugs, novel drug targets including viral assembly, viral transcription, and the movement of the pre-integration complex (PIC) into nuclear etc. are being investigated. Of these, the transcription of the HIV-1 long terminal repeat (LTR) is considered a potential target for blocking HIV-1 replication, because this process is entirely dependent on the HIV-1 transcription factor Tat and is distinguishable from cellular transcription [83]; if a drug targeting this is developed, it could be used as a next-generation antiretroviral drug capable of overcoming the existing resistance problem [84]. Accordingly, a screening system that can discover substances which only inhibit the transcriptional activity of Tat by carefully distinguishing between the transcriptional activity of Tat and that of the host cell was established recently (Fig. 9A) [85]. During a drug repositioning study that used this system, anti-HIV-1 substances targeting the HIV-1 transcription factor Tat, gemcitabine and its two analogs (2'-C-methylcytidine, 3-deazauridine), were discovered (Fig. 9B) [86]. Furthermore, the relevant research has continued to discover novel substances by screening various compound libraries, while a pharmaceuticalization study has been steadily carried out with the aim of using the discovered substances as antiretroviral drugs.

## CONCLUSION

After the discovery of HIV-1 in 1983, the very first HIV therapeutic drug, ZDV, was developed in 1987, followed by the development of about thirty anti-HIV-1 drugs over the subsequent thirty years. Once infected, patients cannot be completely cured of HIV-1 and must take medication for the rest of their life. In this way, HIV-1 is continuously exposed to drugs under a situation in which it cannot be completely eliminated, and resistance-mutations accumulate to avoid this, whereupon a new virus that cannot be controlled by the drug is re-created. To fight against HIV-1 with excellent resistance acquisition, researchers have developed a range of therapeutic targets and made efforts to develop drugs to block HIV-1 ever since the development of the NRTI. In the mid-1990s, PIs such as saquinavir were

developed to inhibit viral mutation, and NNRTIs such as nevirapine were developed to overcome the high frequency of resistance development and the cross-resistance of NRTIs. As more than two types of therapeutic targets have been developed, combination anti-retroviral therapy (cART), which prescribes more than three types of therapeutic target drugs at the same time in order to minimize the development of resistance, has become the general HIV/AIDS treatment. Nevertheless, the virus has not completely disappeared, and the problem of resistance persists due to exposure to continuous drug treatments, which further develop multiple drug resistance. Since the 2000s, researchers have been striving to find novel therapeutic targets to overcome multi-drug resistance. In 2003, enfuvirtide was developed to target the viral penetration process, while maraviroc was developed to competitively inhibit viral attachment to the CCR5 co-receptor in 2007. These drugs also induced various types of resistance, making it necessary to develop even more powerful anti-HIV-1 drugs. Among them, integrase, which incorporates viral nucleic acid into the host chromosome, aroused much interest due to its great potential as a new therapeutic target, and the first integrase inhibitor, RAL, was developed in 2007. This was followed by DTG in 2013, EVG in 2014 and, most recently, BIC and CAB as drug sources for complex medication in 2018 and 2019, respectively. As the battle between HIV-1 and humanity has become increasingly fierce, integrase inhibitor-based long-term active drugs have been developed to reduce the discomfort of taking drugs every day. Also, the humanized antibody IBA, an entirely different type compared to existing drugs, was successfully developed in 2018. Antiretroviral drugs have been developed on a continuous basis, but the latent viral reservoir must be detected and selectively killed if we are to fundamentally and completely cure patients with HIV-1. However, even specific markers for latent viral reservoirs have not yet been discovered. Furthermore, it is expected that another type of resistance could develop soon because INSTIs - currently the most popular type of drugs - were developed on the basis of the chemical structures of existing drugs. Therefore, we should predict new drug-resistance problems with antiretroviral drugs in the future, and therefore must find new therapeutic targets to resolve them. In addition, much greater efforts should be poured into the development of a complete cure technology capable of eliminating the HIV-1 hiding in the host cell from the patient's body, in order to win the final battle between mankind and HIV-1.

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