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Drug Management and Control of the Human Immunodeficiency Virus (HIV)

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Abstract

HIV antiretroviral therapy (ART) is a treatment that uses a combination of medications to manage and control the human immunodeficiency virus (HIV). ART does not cure HIV but reduces the viral load in a person's body to undetectable levels, which prevents the progression of HIV to AIDS and dramatically reduces the risk of transmitting the virus to others. ART typically combines drugs from different classes, such as nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), and integrase inhibitors, to attack the virus at various stages of its life cycle. Starting ART as soon as possible after an HIV diagnosis is crucial, as it helps preserve immune function, reduces the risk of HIV-related complications, and improves overall life expectancy. For individuals who maintain consistent ART, HIV can become a manageable chronic condition, allowing them to lead long, healthy lives. Regular medical check-ups, adherence to the prescribed regimen, and managing potential side effects are essential for the success of ART. Additionally, with advancements in medicine, newer ART options often have fewer side effects and more convenient dosing schedules, including single-pill regimens. Access to ART, along with education and support, is fundamental to improving the quality of life for people living with HIV and reducing new HIV infections globally.

Keywords: Antiretroviral Therapy, Nucleoside Reverse Transcriptase Inhibitors, Human Immunodeficiency Virus, Protease Inhibitors, Integrase Inhibitors

Introduction

The US Centers for Disease Control and Prevention (US CDC) noted the apparent unexpected emergence of a lethal infectious disease among drug users and homosexuals in 1981. The patient's immune system was compromised by this new illness, which resulted in Kaposi sarcoma, Pneumocystis jirovecii pneumonia, lymphoma, and ultimately death. The condition was formerly

known as "Gay Related Immunodeficiency Syndrome" since it was primarily found in male homosexuals at the time of its discovery (GRID). A retrovirus that was eventually identified as the human immunodeficiency virus-1 (HIV-1) was isolated from a lymph node of a lymphoma patient in 1983 by Luc Montagnier and other researchers at the INSTITUT PASTEUR, France [1, 2]. Following this, the viral life cycle was uncovered through numerous investigations, allowing for the quick creation of medicinal drugs and diagnostic technology. Since reverse transcription is the primary feature of HIV-1, a therapeutic drug development method aiming at inhibiting it was first adopted, and zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor, was created in 1987 as the first HIV-1 treatment medication. Following this, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, viral entry inhibitors, and virus integrase strand transferase inhibitors were developed one after the other. In more recent times, improvements have been made to the effects of already-available medications as well as to the creation of a new paradigm of HIV-1 medications. In order to provide a direction for the development of HIV/AIDS therapeutic medications, this study will explore the methods by which these treatments were developed along with more recently created antiviral compounds.

The HIV-1 Replication Steps as the Drug Target

Since HIV-1 was discovered in 1983, its life cycle has been elucidated, and on the basis of research findings, therapeutic medications that suppress HIV-1 multiplication have been produced [3]. HIV-1 interacts to co-receptors (CCR5 or CXCR4) and the CD4 receptor on CD4+ T cells before entering the host cell [4]. Following entry, reverse transcriptase converts the viral RNA genome to DNA, moves it to the nucleus, and integrase fuses it with a host chromosome. The viral transcription factor Tat (Trans-activator of Transcription) and a number of other factors in the host cell work together to express viral mRNA from the inserted viral DNA (provirusIn addition, certain mRNAs are translated into numerous proteins required for the creation of a virion, which encloses the host cell membrane and is expelled from the cell. The whole length of the expressed viral mRNA forms the genome of the progeny virus. Viral protease matures the virion at this point, turning it into an infectious virus that subsequently re-infects the adjacent cells to start a new viral life cycle as shown in Fig 4 below [5]. About 30 HIV-1 therapeutic drugs capable of inhibiting each stage have been created and used in the treatment of HIV-1 patients from the introduction of the first reverse transcriptase inhibitor, ZDV, in 1987 to the most recent integrase strand transferase inhibitor, bictegravir (BIC), in recent years (Fig 5) [5, 6]. Reverse transcriptase inhibitors (nucleoside type and non-nucleoside type), protease inhibitors, integrase strand transferase inhibitors, CCR5 antagonists, and membrane fusion inhibitors are the five categories into which these HIV-1 therapy medications have been divided [5, 6, 7].

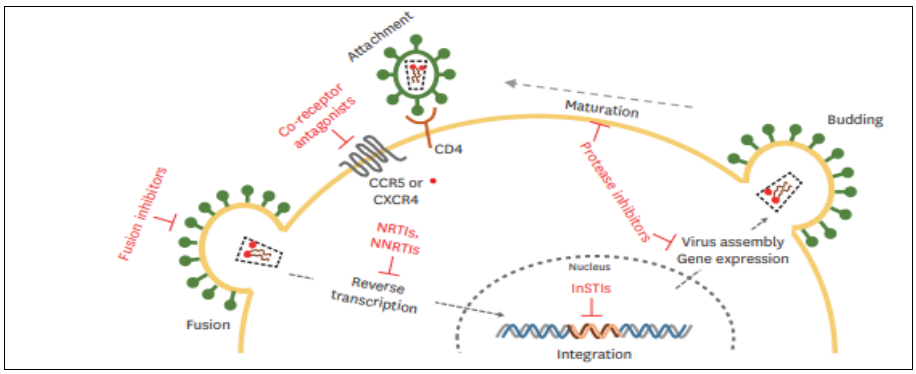

Fig 1: Stages of the HIV-1 life cycle and current target for antiretroviral drugs. HIV-1, human immunodeficiency virus-1; NRTIs, nucleoside analogue reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; InSTIs, integrase strand transferase inhibitors

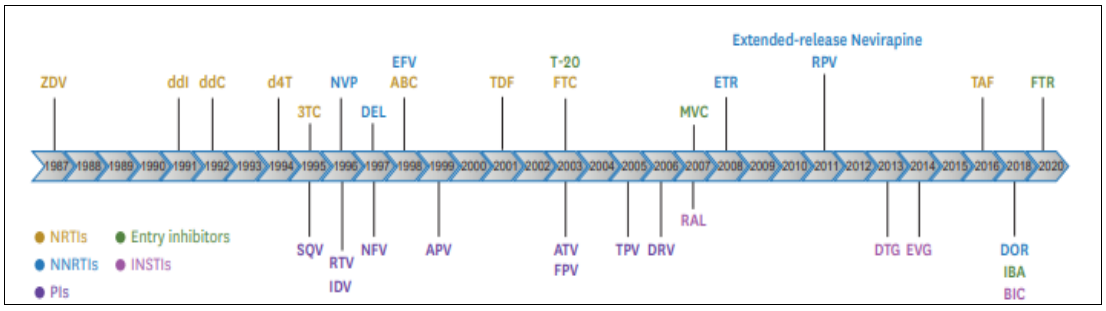

Fig 2: Timeline for FDA-approved antiretroviral drugs. FDA, food and drug administration; ZDV, zidovudine; ddI, didanosine; ddC, zalcitabine; d4T, stavudine; 3TC, lamivudine; SQV, saquinavir; NVP, nevirapine; RTV, ritonavir; IDV, indinavir; DEL, delavirdine; NFV, nelfinavir; EFV, efavirenz; ABC, abacavir; APV, asunaprevir; TDF, tenofovir disoproxil fumarate; T-20, enfuvirtide; FTC, emtricitabine; ATV, atazanavir; FPV, fosamprenavir; TPV, tipranavir; DRV, darunavir; MVC, maraviroc; RAL, raltgravir; ETR, etravirine; RPV, rilpivirine; DTG, dolutegravir; EVG, elvitegravir; TAF, tenofovir alafenamide; DOR, doravirine; IBA, ibalizumab; BIC, bictegravir; FTR, fostemsavir; NRTIs, nucleoside reversetranscriptase inhibitors; NNRTIs, non-nucleoside reverse-transcriptase inhibitors; InSTIs, integrase strand transfer inhibitors; PIs, protease inhibitors

Reverse Transcriptase Inhibitors

The nucleoside reverse transcriptase inhibitor (NRTI) zidobudine (3-azido-3-deoxythymidine, ZDV), the first HIV-1 therapeutic medication, was created in 1987. Since then, numerous NRTIs have been created one after the other [3]. The non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine (NVP), was initially created in 1996 as resistance to nucleoside-like medications rapidly emerged. This was followed by the development of additional NNRTIs [8].

Nucleoside reverse-transcriptase inhibitors (NRTIs)

A class of anti-HIV-1 medications known as NRTIs was given the green light by the US Food and Drug Administration (FDA). The majority of these medications are given as precursors, which subsequently enter the host cell and undergo phosphorylation to take on the nucleotide form, which has the desired effect of a medication [9, 10]. There are currently eight different types of NRTIs in use; most recently, tenofovir alafenamide (TAF), which has improved tenofovir's pharmacological activity, was created and put to use (Table 3) [11]. These medications frequently lack a 3-OH (hydroxyl group) on the deoxyribose moiety of the nucleoside, and as a result, they exhibit an action mechanism during viral DNA synthesis that inhibits viral DNA synthesis by incorporating themselves into the expanding DNA chain and blocking the 3′-5′ phosphodiester bond with the subsequent incoming nucleotide, as shown in Fig 6 [7, 12].

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.

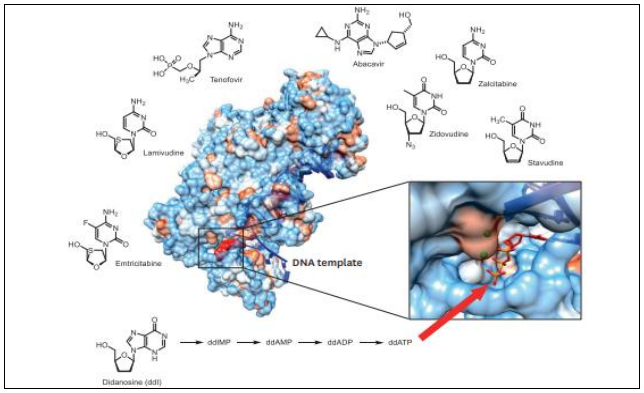

Fig 3: X-ray crystal structure of HIV-1 RT in complex with viral DNA template/primer and Nucleos(t)ide reversetranscriptase inhibitors. A nucleoside inhibitor didanosine (ddI) is converted to ddAMP missing OH, following termination of DNA synthesis by the incoming dTTP. The cartoon of the crystal structure has been adapted from data deposited by Huang *et al*. (1998) [13]. RT, reverse-transcriptase; HIV-1, human immunodeficiency virus-1; DNA, deoxyribonucleic acid; ddAMP, 2′3′-Dideoxyadenosine-5′monophosphate; dTTP, deoxythymidine triphosphate; OH, hydroxyl group

Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)

Contrary to NRTIs, NNTRIs directly bind to the hydrophobic pocket around the reverse transcriptase's active site in order to modify the structure of the enzyme and limit enzymatic activity (Fig 4). NRTIs, on the other hand, operate as a terminator for viral DNA synthesis [7, 12]. They exhibit no cross-resistance with current NRTIs as a result. Despite the fact that these very effective NNRTIs are still being developed today, taking just one dose of them leaves HIV-1 open to developing cross-resistance to additional NNRTIs. As a result, these medications are given along with other anti-HIV-1 medications. Seven of these medication kinds have thus far received approval (Table 4).

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.

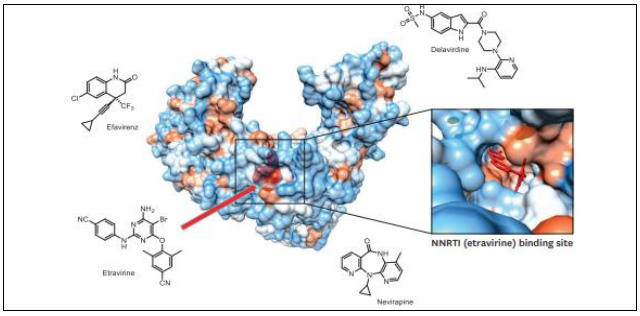

Fig 4: Crystal structure of HIV-1 RT complexed with etravirine and Non-nucleoside reverse-transcriptase inhibitors.The cartoon of the crystal structure has been adapted from Lansdon et. al.,(2010) [14]. HIV-1, human immunodeficiency virus-1; RT, reverse-transcriptase

Protease Inhibitors (PIs)

Numerous protease inhibitors (PIs) against HIV-1 were created after the mid-1990s (Table 5) [15]. The protease of HIV-1 is a crucial enzyme that transforms the precursor proteins of group-specific antigen (GAG) and polymerase (GAG-POL) found in the virion without infectivity into a mature virus with infectivity [16].

Protease inhibitors were therefore warmly welcomed in the field of cutting-edge anti-HIV-1 medications. It was believed that these protease inhibitors would be less likely to develop resistance in the past since this enzyme, which is as small as 11 kDa, is crucial for viral growth. However, resistant mutation was discovered to occur quite frequently in individuals receiving PI medication and was found to be susceptible to cross-resistance, in part because all PIs have chemical structures that are similar for binding to the enzyme's active site [17]. As a result, PIs are currently mostly utilized in "cocktail therapy" alongside three different anti-HIV-1 medications. Additionally, long-term usage of PIs causes the emergence of drawbacks such altered lipid

metabolism and altered lipid distribution in the body. Since the introduction of darunavir in 2006, no new PIs have been created (Fig 8) [7].

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.

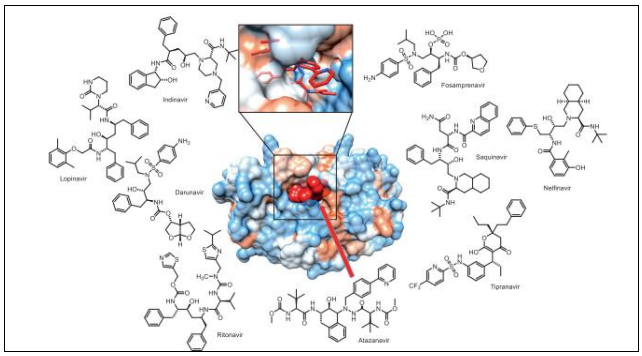

Fig 5: The crystal structure of HIV-1 protease blocked by atazanavir and protease inhibitors. The cartoon of the crystal structure has been adapted from data by King *et al*. (2012) [18]. HIV-1, human immunodeficiency virus-1

Membrane Fusion Inhibitors

In 1997, a study on the crystal structure of glycoprotein 41 (gp41) revealed that it was composed of two helical repeats called heptad repeat 1 (HR1) and heptad repeat 2 (HR2), which interacted to form a six-helix bundle structure from trimeric gp41. As a result, a peptide that could stop this process was created. As evidence, see Fig 9 below [11, 19]. Then, in 2003, the US FDA approved it as enfuvirtide (T-20, Fuzeon), which has primarily been recommended as an injectable therapy for patients who exhibit multi-drug resistance and/or negative side effects while receiving treatment with already-approved medications [20, 21].

CCR5 Antagonists

As seen in Fig 10 below, Maraviroc (MVC), a small-molecule medication created in 2007, is an antagonist of the HIV-1 co-receptor CCR5 [22]. In order to block viral entry into the host cell, it attaches to the CCR5 coreceptor's hydrophobic pocket, alters its conformation, and prevents the viral membrane protein gp120's V3 loop from attaching to CCR5 [23]. Contrary to other anti-HIV medications that bind directly to the virus protein, this medicine targets the co-receptor of the host cell but has been known to develop resistance utilizing a different resistance mechanism [24, 25]. A change in the viral protein gp120's infection route from CCR5 to CXCR4, a strengthening of coherence with CCR5 stronger than maraviroc, and the acquisition of penetrating ability by recognizing the maraviroc-CCR5 complex are some of the ways by which this drug develops resistance [7, 26, 27].

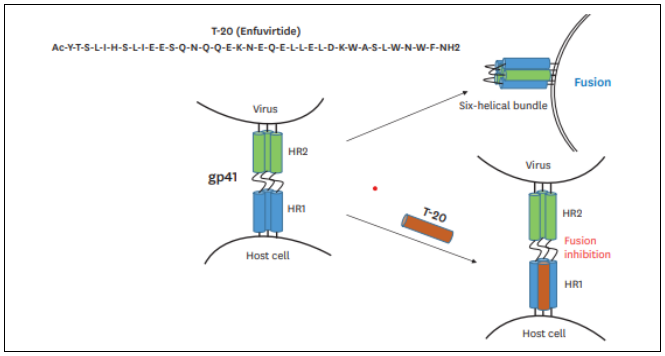

Fig 6: Peptide sequences of T-20 and the mode of action of T-20. The formation of the gp41 six alpha-helix bundle is blocked by T-20 (enfuvirtide) in the final step of the HIV-1 entry process. The cartoon has been adapted from data by Berkhout *et al*. (2012) [28]. HIV-1, human immunodeficiency virus-1

Integrase Strand Transferase Inhibitors (InSTIs)

Viral DNA is integrated into the host chromosome to produce a provirus when reverse transcription is stopped. The virus can then express its own genes and create its offspring from that point on [29]. As a result, integrase is required for the viral DNA to be incorporated into the host chromosome, which is in charge of the crucial phases of the viral life cycle. The most modern HIV-1 medications are directed at this integrase [29]. In order to integrate the viral strand into the host chromosome, the integrase first removes the 3′-OH group from the viral strand [30]. To focus on the role of viral strand transfer among them, integrase inhibitors, also known as integrase (DNA) strand transferase inhibitors (InSTIs), have been created. As shown in Table 8, the first integrase inhibitor to be created was raltegravir (RAL), which was followed by dolutegravir (DTG) in 2013 and elvitegravir (EVG) in 2014 [31, 32]. As shown in Fig 10 below, these medications bind to two magnesium ions that are necessary for the binding of the integrase active site and the viral DNA [7, 33, 34, 35]. This prevents the binding of the integrase active site and the DNAFollowing the phase 3 clinical trial, the US FDA approved BIC in 2018 as a triple complex containing BIC, emtricitabine (FTC), and TAF together with two other types of reverse transcriptase inhibitors [36]. This triple complex demonstrated similar inhibitory effects on virus proliferation during a clinical study as the triple complex DTG/FTC/TAF including DTG, but with fewer negative pharmacological effects [37, 38]. Additionally, BIC is very efficient against the resistance mutation seen in DTG and develops less resistance to it. It has an 18-hour half-life [39, 40].

Table 4: Integrase strand transfer

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

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

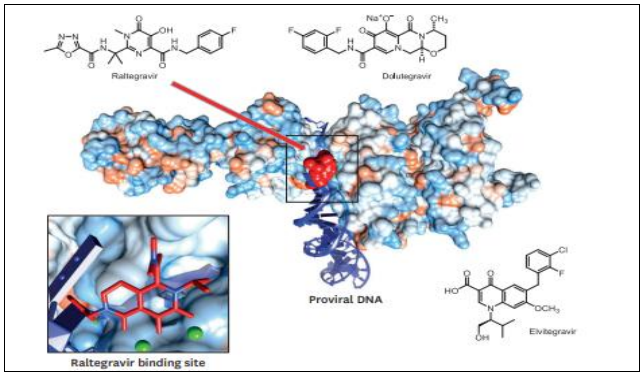

Fig 7: The crystal structure of virus integrase complexed with raltegravir and integrase strand transfer inhibitors

Pharmacokinetic Booster

Cobicistat (COBI), a booster that can raise the plasma concentration and rate of absorption of antiretroviral drugs, was created a number of years ago without possessing any inherent antiviral capabilities [41, 42, 43, 44]. Following an increase in the total absorption of a number of antiretroviral drugs (atazanavir, darunavir, and tenofovir), COBI, a powerful inhibitor of the cytochrome P450 3A enzyme, inhibits intestinal transport proteins. COBI was approved by the US FDA in August 2012 [45]. Instead, it prevents liver enzymes from hydrolyzing the integrase strand transferase inhibitor (InSTI), increasing its effectiveness (36, Lepist *et al*., 2012].

Recent Progress of New Antiretroviral Drugs

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

Long-acting antiviral medications, like cabotegravir and rilpivirine, have been created that have long-lasting effects on the patient's body [46]. Cabotegravir (CAB, GSK744), an InSTI now in development, with a half-life of up to forty days. In contrast, nanoparticle-type nano-suspension typically has a half-life of 21 to 50 days but has the potential to last up to 90 days [47, 48]. Rilpivirine (RPV), on the other hand, is an existing NNTRI. Rilpivirine 25 mg tablets have a half-life of up to 50 days, whereas long-term active nano-suspension has a half-life of up to 90 days [8, 49]. The combined administration of these two drugs kept the virus concentration in the blood below 50 copies/mL in 94 percent of patients who took the drugs at intervals of up to 8 weeks (56 days) and improved patient convenience compared to drugs that were given daily in a recent randomized phase 2b clinical trial. The two-drug combination was submitted to the US and the EU for approval in 2019 following a phase 3 clinical trial investigation. The creation of long-acting medications is anticipated to significantly improve patients' quality of life because they only need to take them occasionally [50, 51, 52]. As an alternative, beginning in 2020, the injectable long-acting CAB is being studied for pre-exposure prophylaxis (PrEP) in males who are HIV-uninfected as part of HPTN083 (HIP Prevention Trials Network 083).

2. Doravirine (DOR)

DOR is a next-generation NNRTI that was approved by the US FDA in August 2018 for the treatment of HIV-1 that is multi-drug resistant [53]. While its negative effects on the central nervous system (CNS) are essentially nonexistent, it rarely exhibits a drug-drug interaction when paired with other anti-HIV-1 medications and exhibits a lower level of LDL compared to other anti-HIV-1 drug groups [54, 55]. According to the findings of a follow-up survey, the FDA clearance is receiving a lot of attention [56, 57].

3. In the body, FTR is converted to temsavir (TMR), which binds to the virus' gp120 and prevents HIV-1 from entering the host cell by preventing interaction with the co-receptors CCR5 and CXCR4 [58, 59]. There haven't been any reports of cross-resistance with other antiretroviral medication classes [58, 59, 60, 61]. In July 2020, the US FDA authorized FTR for the treatment of HIV-1 that is multidrug resistant.

4. Ibalizumab (IBA)

IBA is a monoclonal immunoglobulin G4 antibody that has been humanized and has a high affinity for the host cell's CD4 [62, 63]. By using the co-receptor CCR5 or CXCR4, it successfully prevents HIV-1 from entering the host cell. Additionally, it exhibits a therapeutic impact against multi-drug resistant viruses already in existence [62]. The US FDA authorized it in March 2018 for the treatment of HIV-1 that is multidrug resistant, and it is administered intravenously every 14 days [64, 65]. It has been suggested for potential use in combination therapy with additional anti-retroviral medications, such as InSTI, PI, and NRTI/NNRTI, all of which have an anti-retroviral effect that differs from IBA [65, 66].

Islatravir

Islatravir has several modes of action and is being investigated as a nucleoside reverse transcriptase translocation inhibitor for HIV-1 prophylaxis [67]. When compared to other NRTIs, islatravir has a 4-fold lower IC50 and a longer plasma half-life (120 hours). It also has a larger inhibitory impact against NRTI mutations, such as M184I/V, K65R, and K70E. Using a two-drug fixed dose combination of DOR and islatravir, it is being evaluated as an HIV-1 therapy and PrEP in its third phase of development [68].

GS-6207

A tiny chemical called GS-6207 prevents the HIV-1 capsid protein from folding. It interferes with the interaction between the capsid protein and cellular cofactors like Nup153 and CPSF6, which is necessary for several stages of the viral replication cycle, by binding firmly at a conserved interface between capsid protein monomers. In Phase 1 clinical investigations, monotherapy with a subcutaneous dosage of GS-6207 (450 mg) demonstrated sustained anti-viral active concentrations for more than 6 months and a mean 2.2 log reduction of the viral load at day 10. GS-6207 has been suggested as a robust long-acting medication to cure or prevent HIV-1 infection because of its potency [69].

Viral transcription factor Tat as therapeutic target

Novel pharmacological targets, including as viral assembly, viral transcription, and the migration of the pre-integration complex (PIC) into nuclear, are being researched to overcome HIV-1 treatment resistance. One of these is the transcription of the HIV-1 long terminal repeat (LTR), which is thought to be a potential target for preventing HIV-1 replication because it is entirely dependent on the HIV-1 transcription factor Tat and can be distinguished from cellular transcription [70]. If a drug targeting this is created, it could be used as a next-generation antiretroviral drug capable of resolving the issue of resistance currently present [71]. Thus, by carefully differentiating between the transcriptional activity of Tat and that of the host cell, a screening approach that can find compounds that only

inhibit the transcriptional activity of Tat was recently constructed [72]. Gemcitabine and its two analogs (2′-C-methylcyitidine, 3-deazauridine) were shown to target the HIV-1 transcription factor Tat during a medication repositioning research using this method [73]. A pharmaceuticalization study has been steadily conducted with the goal of employing the identified chemicals as antiretroviral medications, and relevant research has continued to identify novel substances by screening diverse compound libraries.

In summary, the first HIV therapeutic treatment, ZDV, was created in 1987 following the identification of HIV-1, and throughout the course of the next 30 years, roughly 30 other anti-HIV-1 medications were created. Once infected, persons with HIV-1 must take medication for the rest of their lives because the disease cannot be entirely cured. In order to escape being entirely eradicated, resistance-mutations build when HIV-1 is continually exposed to medications in this way. As a result, a new virus that is uncontrollable by the drug is subsequently formed. Since the development of developed to inhibit viral mutation, researchers have worked to develop drugs to block HIV-1 and have developed a variety of therapeutic targets. NNRTIs, like nevirapine, were developed to overcome the high frequency of resistance development and the cross-resistance of NRTIs. Combination anti-retroviral therapy (cART), which prescribes more than three types of therapeutic target medications concurrently in order to minimize the development of resistance, has become the standard HIV/AIDS treatment as more than two types of therapeutic targets have been identified. However, the virus is still present, and resistance issues still exist as a result of repeated drug treatments that further breed multiple drug resistance. To combat multi-drug resistance, researchers have been searching for new therapeutic targets since the 2000s. Enfuviritide, which was created in 2003 to target the viral penetration procedure, and maraviroc, which was created in 2007 to competitively limit viral attachment to the CCR5 co-receptor. Additionally, these medications caused various forms of resistance, necessitating the creation of progressively more potent anti-HIV-1 medications. Due to its significant promise as a new therapeutic target, integrase, which inserts viral nucleic acid into the host chromosome, attracted a lot of attention. The first integrase inhibitor, RAL, was created in 2007 DTG, EVG, and, most recently, BIC and CAB as drug sources for complicated medications in 2018 and 2019, respectively, came after this. Long-term active HIV-1 medications based on integrase inhibitors have been developed to lessen the discomfort of daily medication use as the fight against HIV-1 has grown more intense. Also, the humanized antibody IBA, an altogether distinct kind compared to existing medicines, was successfully produced in 2018. Antiretroviral medications have been produced on a continual basis, but the latent virus reservoir must be discovered and selectively eliminated if we are to fundamentally and totally treat people with HIV-1. Even Nevertheless, there are currently no known precise markers for latent viral reservoirs. Furthermore, because InSTIs—the current most popular class of medications—were created based on the molecular structures of preexisting drugs, it is anticipated that another sort of resistance may soon emerge. Therefore, we should anticipate more antiretroviral drug resistance issues in the future and develop novel treatment targets to address them. In order to win the final conflict between humanity and HIV-1, considerably more effort should be put into developing a complete cure technology capable of eradicating the HIV-1 hiding in the host cell from the patient's body.

Conclusion

HIV antiretroviral therapy (ART) has transformed HIV from a fatal disease to a manageable chronic condition, improving patients' quality of life and reducing transmission. Adherence to ART suppresses viral load, boosts immunity, and prevents progression to AIDS, making it essential for both individual health and broader public health efforts in combating HIV.

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