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EDITORIAL
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Four decades of continuing innovations in the development of antiretroviral therapy for HIV/AIDS: Progress to date and future challenges

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Abstract: The treatment of HIV-1 infection and AIDS represents one of the greatest challenges in medicine. While there is no cure for HIV/AIDS, truly remarkable progress has been made for treatment of HIV/AIDS patients today. The advent of combination antiretroviral therapy (cART) in the mid-1990s dramatically improved HIV-1 related morbidity, greatly prolonged life expectancy, and delayed progression of AIDS. Due to current antiretroviral therapy, the mortality rate for HIV infected patients is closely approaching the mortality rate for the general population. The long-term success of HIV-AIDS treatment requires continued enhancement of cART with further development of novel drugs that would exhibit fewer side effects, higher genetic barrier to the development of resistance, and longer action with durable virologic suppression. This editorial article provides a quick review of four decades of intense drug development research efforts targeting various viral enzymes and cellular host factors leading to the evolution of today's treatment of patients with HIV-1 infection and AIDS. It also touches on challenges of future treatment options.

***Keywords*:** AIDS, antiretroviral, HIV, therapy, drug development

It has been four decades now, since the human immunodeficiency virus (HIV), the etiological agent for acquired immunodeficiency syndrome (AIDS), was identified. The first reported case was recorded in 1981. According to the UNAIDS/WHO's report on HIV/AIDS, to date, an estimated 38.4 million patients worldwide have been living with HIV-1 infection and AIDS. Also, an estimated 40.1 million people lost their lives due to HIV and AIDS-related illness since the beginning of the epidemic (*1*). These figures are quite staggering by any measure. Since the early years of the HIV/AIDS epidemic, there has been an unprecedented effort among scientific communities around the world to control the virus with particular emphasis on translation of basic science into the development of antiretroviral therapeutics. This has resulted in intense collaboration between research communities in academic and pharmaceutical laboratories, doctors and health care providers, public health officials, funding agencies, and HIV/AIDS patients. It is a truly remarkable alliance in the history of medicine. The development of novel therapeutic agents and implementation of drug combinations targeting various steps of the HIV life cycle has transformed HIV infection and AIDS from an irrefutably fatal disease into a manageable chronic ailment. However, there is no cure for HIV infection or AIDS yet. The introduction of antiretroviral therapy (ART) dramatically suppressed HIV replication in most patients with HIV infection and AIDS who receive an ART treatment regimen. The clinical outcome then resulted in a significant decline of HIV/AIDS-related mortality, particularly in developed countries where patients have access to potent antiretroviral drug combinations (*2*). The progression and continuous development of new and more effective antiretroviral therapies for the treatment of HIV/AIDS is also an inspiring testament in modern medicine where synthetic organic and innovative medicinal chemistry played a very critical role in the design, development, and evolution of innovative antiretroviral drugs.

In early days of the 1980s, HIV/AIDS patients had a life expectancy of about one year, following the diagnosis. The first drug treatment for HIV/AIDS patients began in 1987 when a failed anticancer drug from the 1960s, azidothymidine (AZT), also referred as zidovudine (ZDV, Figure 1), was shown to potently inhibit a viral enzyme reverse transcriptase (RT) (*3,4*). RT catalyzes the transcription of double stranded viral RNA into DNA, an essential step in the viral replication process. This nucleoside reverse transcriptase

inhibitor (NRTI) gets phosphorylated *in vivo* and blocks enzymatic function of RT by incorporating the nucleotide analog and causing chain termination. AZT suppressed HIV replication, reduced opportunistic infection, and extended lives of HIV/AIDS patients. AZT marked the first drug treatment for HIV/AIDS patients. Other NRTI such as, didanosine (ddI) and dideoxycytidine (ddC) were subsequently approved in the early 1990's. These RT inhibitor drugs proved useful however, toxicity and resistance development compromised their effectiveness (*5*). The approval of AZT and other NRTIs paved the way for development of several new classes of antiretroviral therapies targeting other critical viral targets. Also, development of several effective HIV diagnostic tests, particularly those measuring viral loads and CD4+ cell counts further accelerated the drug development process.

The breakthrough in the development of novel antiretroviral therapeutics targeting other biochemical mechanisms occurred in the mid-1990s. The approval of HIV-1 protease inhibitor drugs marked the beginning of a new era of HIV/AIDS treatment. Protease inhibitor research efforts also became a hallmark of innovation in modern drug discovery and medicinal chemistry. Early knowledge of virus replication established that HIV-1 protease plays a critical role in processing the *gag* and *gag-pol* gene product into essential viral proteins including protease, reverse transcriptase, integrase, and other important structural proteins. Not surprisingly, HIV protease was recognized as an important biochemical target for drug development, early on. Consequently, a significant effort towards design, discovery, and development of HIV-1 protease inhibitor drugs then intensely followed in both academic and pharmaceutical laboratories. The HIV-1 protease is an aspartic acid protease. It is a homodimeric enzyme with two 99-amino acid subunits with each monomer contributing a catalytic aspartic acid functional group to form the active site. The human genome features several other aspartic acid proteases that play critical roles in the pathogenesis of human diseases. Previous drug discovery efforts against these aspartic acid proteases included renin inhibitor design for treatment of hypertension. Early work on renin inhibitors did not translate into any approved drugs however, it provided important groundwork in terms of mechanism-based design for HIV-1 protease inhibitors. The challenging goals of HIV-1 protease inhibitor design were to develop selective, metabolically stable, and orally bioavailable inhibitor drugs. A massive research effort in academic and pharmaceutical laboratories began with the goal of developing HIV-1 protease inhibitor drugs.

The first HIV-1 protease inhibitor drug, saquinavir (SQV, Figure 2) received FDA approval in the mid-

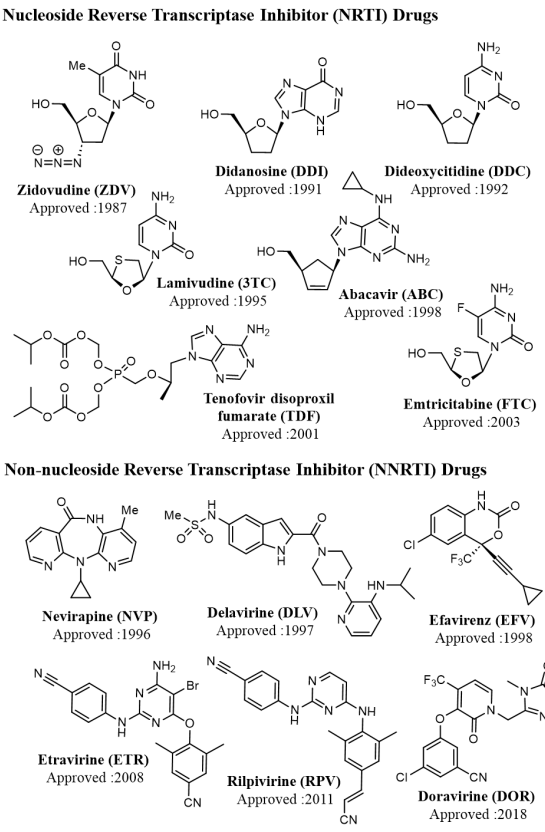

Figure 1. Structures of approved RT inhibitor drugs.

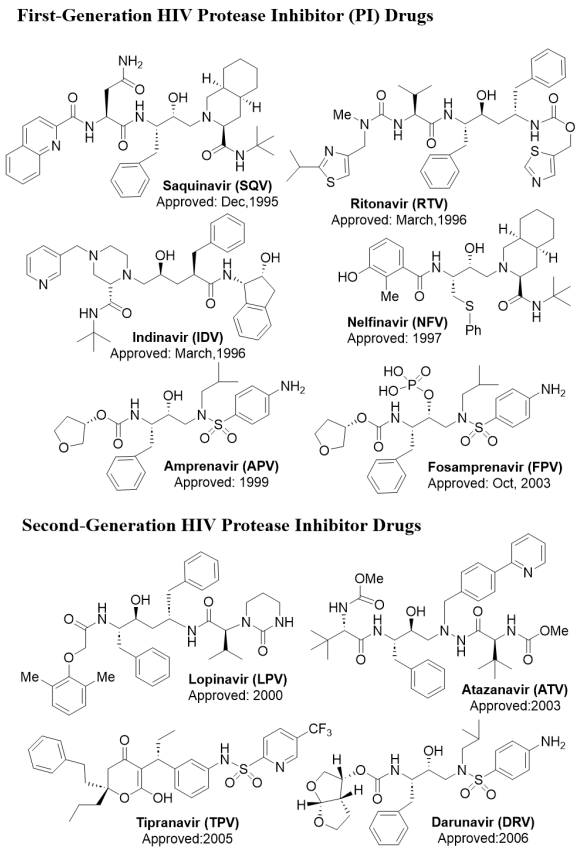

Figure 2. Structures of approved HIV-1 protease inhibitor drugs.

1990s (*6,7*). Subsequently, other protease inhibitor drugs, such as ritonavir followed by indinavir, and nelfinavir were approved by the FDA. These protease inhibitors were then incorporated into highly active antiretroviral therapy (HAART) with reverse transcriptase inhibitor drugs developed earlier. The HAART treatment regimens have had dramatic impact on management of HIV-1 infection and suppression of HIV-1 replication in treated patients. This led to a significant improvement in life expectancy and mortality rates of HIV/AIDS patients who have access to these therapies in developed countries. The HAART treatment regimens immensely improved the prognosis of the AIDS epidemic by transforming HIV/AIDS into a manageable chronic disease (*8,9*). Despite this major progress, early PI-based therapies were often rendered ineffective due to emergence of drug-resistant HIV-1 variants. Therefore, a second generation of nonpeptide protease inhibitor drugs such as atazanavir, lopinavir, tipranavir and darunavir was developed to address these issues. The last approved protease inhibitor drug darunavir (2006) is a widely used PI-drug. Darunavir, is highly potent and has been shown to be particularly effective in treatment of patients harboring drug-resistant HIV-1 variants (*10,11*).

In the mid-1990s another class of antiretroviral drugs, called non-nucleoside reverse transcriptase inhibitor (NNRTI) was developed (*12,13*). Unlike NRTIs, NNRTIs do not require *in vivo* phosphorylation to exert their inhibitory activity. This drug class includes nevirapine and efavirenz. They block HIV replication by noncompetitive inhibition of RT and bind to a hydrophobic pocket in the subdomain of p66, located 10Å away from the active site of RT, known as the NNRTI pocket. Subsequently, other NNRTI drugs such as etravirine, rilpivirine, emtricitabine and doravirine were developed. These drugs along with a newer class of NRTIs such as abacavir, tenofovir, lamivudine and emtricitabine were effectively utilized in various combination therapies to control HIV-1 infection and AIDS.

Drug discovery efforts targeting viral entry led to the development of a new class of drugs. As mentioned earlier, HIV-1 replication is a multistage process where viral attachment and viral fusion are critical early stages of the replication cycle. Viral attachment involves interaction of the viral gp120 protein with the CD4 protein on the surface of the T-cell. HIV enters the T-cell by a fusion process, which is facilitated by the viral protein gp41 and the CCR5 and CXCR4 coreceptors on the T-cell. Both the viral entry and viral fusion have been targeted to block the viral replication cycle. The first entry inhibitor enfuvirtide received FDA approval in 2003. Enfuvirtide (T-20, Figure 3) is a 36 amino-acid synthetic peptide (*14*). It mimics amino acids 127–162 which is located in heptad repeat-2 (HR-2) in the HIV gp41 envelope glycoprotein subunit. Its mechanism of action involves binding to the residues in HR-1 and blocking a conformational change in gp41 necessary for fusion of the lipid envelope of HIV with the membrane of CD4 T cells, thus preventing viral entry. It was developed to target gp41 protein as an injectable drug. The second entry inhibitor is maraviroc approved in 2007 (*15*). This drug blocks the interaction of HIV-1 gp120 protein with the CCR5 coreceptor on the target cell. Maraviroc is used in combination with other anti-HIV drugs. HIV-1 can use other coreceptors for viral entry and maraviroc may not be effective for all patients. Therefore, an HIV-1 tropism test is necessary to determine if the drug would be useful for a particular patient group.

The latest class of approved anti-HIV drugs is Integrase strand transfer inhibitors (INSTIs) (*16,17*). The first orally active integrase inhibitor drug raltegravir (Figure 3) was approved in 2007. HIV-1 integrase is a key enzyme involved in integration of proviral DNA created by reverse transcriptase into host T-cell DNA by formation of a covalent bond between viral DNA and host T-cell DNA. In essence, blocking of integrase enzyme function would prevent incorporation of viral DNA into host cell DNA, an essential step for viral replication. Inhibition of this vital step has also been recognized as a critical target for drug development. Since approval of the first INSTI drug raltegravir in 2007, other INSTIs such as elvitegravir in 2012, dolutegravir in 2013, and cabotegravir in 2021 were approved for treatment of HIV/AIDS patients. Introduction of the antiretroviral agents in cART led to excellent suppression of HIV-1 replication in the vast

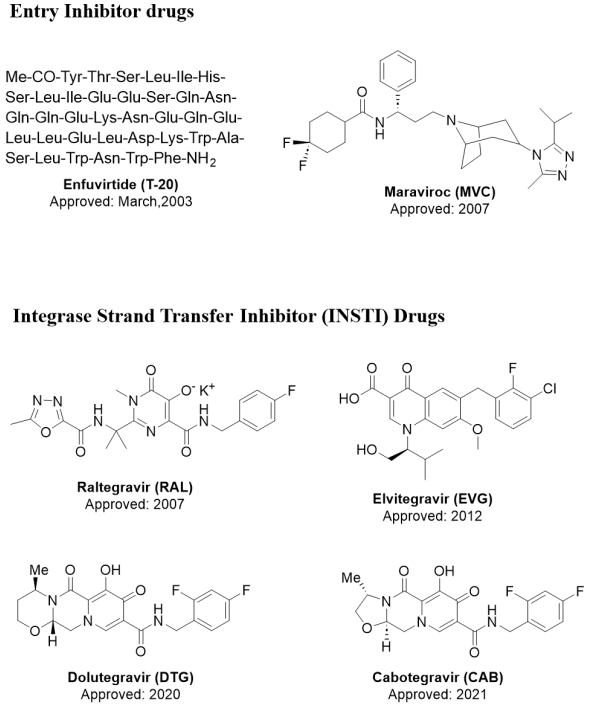

Figure 3. Structures of approved entry inhibitor and integrase inhibitor drugs.

majority of HIV/AIDS patients.

To date, more than 30 anti-HIV drugs targeting many different viral replication mechanisms have been approved (*18*). These drugs provide many choices to individualize drug treatment. Due to issues related to safety, tolerability, pill burden, and dosing frequency, not all approved drugs are used clinically. Current less toxic and more efficacious treatment regimens evolved from the earlier grueling experience of large pill burden, drug toxicities, drug-drug and food-drug interactions, inadequate viral suppression, and emergence of drug-resistant variants. Today, multidrug combinations are the key to suppress viremia and delay emergence of drug resistance. cART needs to continue indefinitely as even a temporary halt in cART results in rapid viral rebound in almost all patients due to the persistence of viral reservoirs in HIV infected patients. The use of older NRTIs is limited due to severe mitochondrial, bone marrow toxicities, and peripheral neuropathy (*19*). The first-generation protease inhibitors drugs paved the way for cART treatment regimens with RT inhibitor drugs, which changed the course of the HIV epidemic dramatically. However, their use has been limited due to poor drug properties, ranging from peptide-like features, low oral bioavailability, metabolic instability, PI-associated lipodystrophy, and other side effects. More potent and less toxic, second-generation PI-drugs are mostly used clinically. Interestingly, the first-generation PI drug, ritonavir however is used in low doses with other PI drugs as a pharmacokinetic booster. Low doses of ritonavir are ineffective against HIV, but they inhibit the CYP-3A4 metabolizing enzyme, improves oral bioavailability and duration of action of other PI drugs. The viral entry inhibitor, enfuvirtide is a large synthetic peptide with a short plasma half-life. While it is an effective antiretroviral agent, its clinical use is limited as the drug needs to be injected subcutaneously, twice daily and often results in side effects at the injection sites. The other entry inhibitor maraviroc is a CCR5 antagonist which is approved for both treatment of naïve and treatment experienced patients by blocking R5-tropic HIV entry into CD4 cells. However, its clinical use is limited as the drug requires inconvenient tropism testing and needs twice daily dosing (*20*).

The development of drug resistance represents one of the major causes of HIV treatment failure. At present, boosted second generation protease inhibitors and integrase inhibitor drugs have shown efficacy leading to sustained viral suppression and improved clinical benefits. Among protease inhibitors, boosted darunavir has been shown to be particularly effective. It has shown higher genetic barriers for resistance development compared to other available agents. Darunavir was developed through structure-based design efforts by promoting extensive hydrogen bonding interactions with the highly conserved active site protease backbone atoms. This 'backbone binding concept' turned out to be an effective strategy for combating drug-resistant HIV variants (*21*). Since entry inhibitor drugs interfere with an earlier viral replication step of infection compared to cART, the development of cross-resistance to cART agents is not expected. Both viral entry inhibitor drugs, enfuvirtide and maraviroc are approved for treatment of multidrug resistant HIV strains but their use has been limited. Currently approved integrase inhibitor drugs are effective anti-HIV agents in cART treatment regimens. Among these, dolutegravir has shown a high genetic barrier for resistance development compared to other INSTs, raltegravir and elvitegravir (*22*).

The past four decades of HIV-AIDS drug development efforts targeting various viral enzymes and cellular host factors involved in the HIV-1 replication cycle, led to significant advances in today's HIV-AIDS treatment. While there is no cure for HIV/AIDS, the combination antiretroviral therapy (cART) significantly improved HIV-1 related morbidity, greatly prolonged life expectancy, and delayed or prevented progression of AIDS. In the absence of a cure, the long-term success of HIV-AIDS treatment will require continuation of cART with durable virologic suppression without the emergence of drug-resistant variants. Therefore, current, and future priorities remain to develop more efficacious drugs and develop new drugs targeting novel viral mechanisms to further improve cART regimens with reduced toxicities, improved tolerability, decreased pill burden and extended duration of action. Also, it is critically important to develop innovative therapies that not only improve efficacy and safety over the existing drugs but also delay or prevent the development of drug-resistant HIV-1 variants. Despite much improvement in cART regimens in recent years, HIV-associated neurocognitive disorders, dementia-like symptoms, are increasing at an alarming rate due to viral reservoirs in the CNS and brain. New drug development needs to target persistent HIV reservoirs in the CNS, peripheral blood, and lymphoid tissues. While complete eradication of HIV and a cure appears to be a formidable challenge, the development of more effective cART regimens addressing these issues with the goal of eradication of viral reservoirs, forms an important step forward.

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Conflict of Interest: The author has no conflicts of interest to disclose.

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