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EVOLUTION OF ANTI-HIV DRUG: PAST, PRESENT, CHALLENGES, RECENT ADVANCEMENT& FUTURE PROMISES

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ABSTRACT

Infection with the Human Immunodeficiency virus (HIV) is now considered a chronic condition. Despite the fact that highly active antiretroviral therapy has proven to be effective, a number of difficulties remain. Because the treatments can't completely eradicate the virus, there's no cure yet,and patients must stick to their treatment regimen for the rest of their lives, risking toxic side effects, drug-drug interactions, and drug resistance. The development of a large number of effective antiretroviral medications has been aided by a comprehensive understanding of viral replication and its interaction with host cell components (ARVs). New medications of the same class, such as apricitabine, elvucitabine, and etravirine, have showed promise against HIV strains resistant to first-line therapy. These medications have given patients with drug-resistant diseases a new option. However, the long-term impact of their use on safety has yet to be determined. CD4 receptor attachment inhibitors, maturation inhibitors, pharmacokinetic enhancers, capsid assembly inhibitors, and lens epithelium derived growth factor inhibitors are among the novel medications still in development. ARVs, particularly tenofovir and emtricitabine, are currently being studied for the prevention of HIV-1 sexual transmission. The initial results of an HIV prevention trial network are favourable and have advised the use of ARVs for pre-exposure prophylaxis. As a result, ARVs are an important part of the HIV prevention and treatment strategy. This review article addresses the difficulties of treating HIV-1 and provides an update on many key advances in the development of antiretrovirals (ARVs).

KEYWORDS: HIV, ARV, Prophylaxis, Pharmacokinetic enhancer, CD-4 receptor, Drug resistant.

1.1. INTRODUCTION

Major breakthroughs in our understanding of HIV replication and pathogenesis have enabled the discovery of various therapeutic targets. As a result, there are currently a variety of antiretroviral (ARV) drugs accessible. Antiretroviral therapy (ART) has developed from monotherapy with azidothymidine (AZT) to a combination of two ARVs, such as nucleoside reverse transcriptase inhibitors (NRTIs) and highly active antiretroviral therapy (HAART). Immunological condition, quality of life, and HIV-related morbidity and mortality have all improved significantly as a resultof the triple therapy. After the development of many therapeutic regimens, the disease state has changed from a "virtual death sentence" to a "chronic manageable ailment." The constant search for new drug combinations, as well as the preference for switching first-line therapies and the discovery of newer pharmaceuticals, has all contributed to the development of newer drugs.[1] Hull MW and Montaner J. (2011).

However, the medicine treatment's success comes at the cost of life-threatening side effects, drug- drug combos, and lifetime therapy's uncomfortable nature. Numerous patients who have receivedtreatment for the disease have experienced drug toxicity or are in danger of treatment failure due to multi-drug resistance since the disease has entered its third decade.

Furthermore, the prevention of HIV infection through sexual interaction has received a lot of attention. The Evolution of ARV Drugs: Past, Present, and Future for HIV Treatment and Prevention is the subject of this article review, which seeks to cover all of the relevant points. Thisresearch also looks at HIV-1 treatment issues and gives an update on recent breakthroughs in ARV research.[2] Johnson VA, *et al*. (2008).

1.2. HIV

The human immunodeficiency virus (HIV) is a virus that causes infection in humans. The human immunodeficiency virus (HIV) is an infection that affects CD4 cells, which are a type of T cell. AIDS (acquired immunodeficiency syndrome) is a disease caused by the human immunodeficiency virus (HIV)

Fig 1.1.

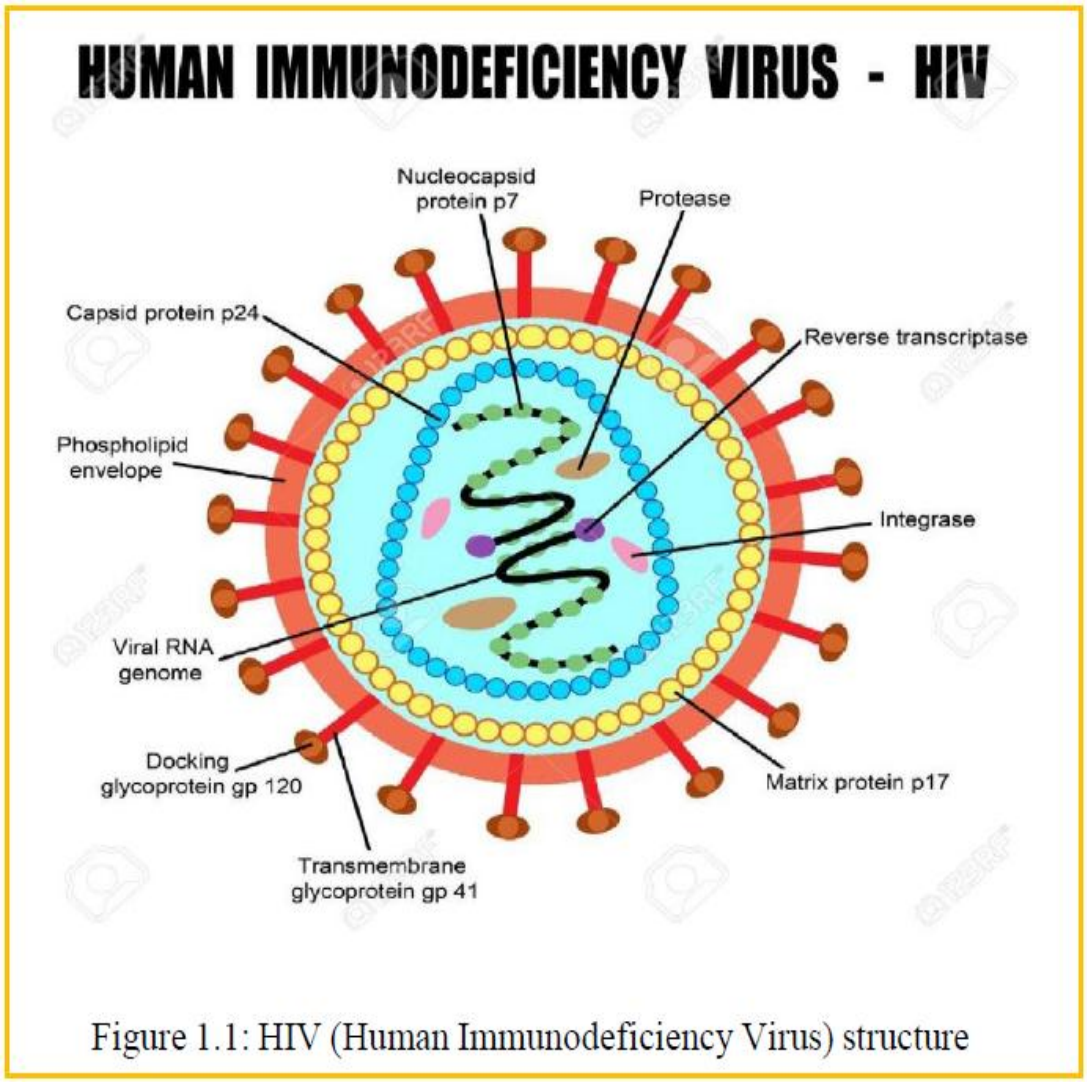

Figure 1.1: HIV (Human Immunodeficiency Virus) structure

HIV is a single stranded RNA retrovirus which uniquely carries out reverse transcription of proviral DNA from viral RNA (normally RNA is transcripted from DNA) with the help of a viral RNA- dependent DNA polymerase (reverse transcriptase). The primary cell type attacked by HIV is the CD4+ helper T-lymphocyte, but later macrophages and some other cell types may also be infected.

When population of CD4 cells declines markedly (<200 cells/μL), cell mediated immunity (CMI) is lost and opportunistic infections abound, to which the victim ultimately succumbs, unless treated. Because the HIV genome integrates with the host DNA, eradication of the virus from the body of the victim appears impossible at present.[3] Kapila A, *et al.* (2016)

There is no cure of AIDS but there are certain medicines which are used to slow down the diseases so you stay healthier for long time. HIV is a lifelong infection. However, receiving treatment and managing the disease effectively can prevent HIV from reaching a severe level and reduce the risk of a person passing on the virus.[4] Bhatti AB, *et al.* (2016)

1.2.1. Causes of HIV

HIV infection is caused by the human immunodeficiency virus. You can get HIV from contact with infected blood, semen, or vaginal fluids are:

i. Most people get the virus by having unprotected sex with someone who has HIV.
ii. Another common way of getting it is by sharing drug needles with someone who is infectedwith HIV.
iii. The virus can also be passed from a mother to her baby during pregnancy, birth, orbreastfeeding.
iv. HIV doesn't survive well outside the body. So it can't be spread by casual contact like kissing or sharing drinking glasses with an infected person.[5] Malani PN, *et al.* (2016)

1.2.2. HIV Diagnosis

Table-1.1: HIV-1, HIV type 1; HIV-2, HIV type 2.[6] Deeks, *et al.* (2015).

Test Type	Measurement	Notes	Eclipse period*
First generation	IgG against viral lysate	HIV-1 western blot and HIV-1 immunofluorescence assay	4–7 weeks
		Assay is being phased out	
Second generation	IgG against synthetic peptides or recombinant proteins	Most rapid tests use second-generation technology	4–7 weeks
		Can differentiate HIV-1 infection from HIV-2 infection	
Third generation	IgG and IgM against synthetic peptides or recombinant proteins	Same technology as fourth-generation assay, but is less sensitive	3–5 weeks
		Assay is being phased out	
Fourth generation	IgG and IgM against synthetic peptides or recombinant proteins, and monoclonal antibodies against p24	Recommended as an initial diagnostic test for HIV infection	2–3 weeks
Nucleic acid testing	Detection of HIV-1 RNA	Might not detect HIV-2 infection	10 days

1.2.3. Global HIV & AIDS statistics — 2019 fact sheet

Table 1.2: Global HIV & AIDS statistics — 2019 fact sheet.

Column	2000	2005	2010	2012	2014	2015	2016	2017	2018/*-2019
People living withHIV(million)	24.9	28.5	31.7	33.2	34.8	35.6	36.4	37.2	37.9
New HIVInfections (total)in (million)	2.8	2.4	2.1	2.0	1.9	1.9	1.8	1.8	1.7
New HIVinfections (aged15+) in (million)	2.3	2.0	1.8	1.8	1.7	1.7	1.7	1.6	1.6
New HIVinfections (aged0–14) in (10000)	450 000	410 000	280000	230000	200000	190000	180000	170000	160000
AIDS-related deaths in (million/1000)	1.4	1.7	1.2	1.0	920000	880000	840000	800000	770000
People accessingantiretroviral therapy* in (million/1000)	576 000	2.0	7.7	11.2	15.1	17.0	19.1	21.3	*24.5 / 23.3

*Note- As of end of June 2019, 24.5 million [21.6 million–25.5 million] people were accessingantiretroviral therapy.

1.2.3.1 New Global HIV Statistics--- 2021 fact sheet

1. 28.2 million people were accessing antiretroviral therapy as of 30 June 2021.
2. 37.7 million [30.2 million–45.1 million] people globally were living with HIV in 2020.
3. 1.5 million [1.0 million–2.0 million] people became newly infected with HIV in 2020.
4. 680 000 [480 000–1.0 million] people died from AIDS-related illnesses in 2020.
5. 79.3 million [55.9 million–110 million] people have become infected with HIV since the start of the epidemic.
6. 36.3 million [27.2 million–47.8 million] people have died from AIDS-related illnesses since the start of the epidemic.

1.2.3.2 People living with HIV

1. In 2020, there were 37.7 million [30.2 million–45.1 million] people living with HIV.
2. 36.0 million [28.9 million–43.2 million] adults.
3. 1.7 million [1.2 million–2.2 million] children (0–14 years).
4. 53% of all people living with HIV were women and girls.
5. 84% [67– >98%] of all people living with HIV knew their HIV status in 2020.
6. About 6.1 million [4.9 million–7.3 million] people did not know that they were living withHIV in 2020.

1.2.3.3 Key populations

1.2.3.3.1 In 2020, key populations (sex workers and their clients, gay men and other men who have sex with men, people who inject drugs, transgender people) and their sexual partners accounted for 65% of HIV infections globally:

1. 93% of new HIV infections outside of sub-Saharan Africa.
2. 39% of new HIV infections in sub-Saharan Africa.

1.2.3.3.2. The risk of acquiring HIV is:

1. 35 times higher among people who inject drugs.
2. 34 times higher for transgender women.
3. 26 times higher for sex workers.
4. 25 times higher among gay men and other men who

have sex with men.[7] Global HIV &AIDS statistics — 2020 fact sheet, UNAIDS.

5.

1.2.4. HIV Medication

Table 1.3: HIV Drug Classification[8] Jonathan E. Kaplan (2019).

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)	NRTIs force the HIV virus to use faulty versions of building blocks so infected cells can't make more HIV.	Abacavir, Emtricitabine, Lamivudine, Stavudine, Tenofovir alafenamide, Tenofovir disoproxil fumarate, Zidovudine
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	These are also called "non-nukes." NNRTIs bind to a specific protein so the HIV virus can't make copies of itself, similar to jamming a zipper.	Delavirdine, Doravirine, Efavirenz, Etravirine Nevirapine, Rilpivirine
Protease Inhibitors (PIs)	These drugs block a protein that infected cells need to put together new HIV virus particles.	Atazanavir Darunavir Fosamprenavir, Indinavir Lopinavir + ritonavir, Nelfinavir, Ritonavir Saquinavir Tipranavir
Integrase Inhibitors	These stop HIV from making copies of itself by blocking a key protein that allows the virus to put its DNA into the healthy cell's DNA. They're also called integrase strand transfer inhibitors (INSTIs).	Bictegravir Dolutegravir Elvitegravir Raltegravir
Fusion Inhibitors	Unlike NRTIs, NNRTIs, PIs, and INSTIs -- which work on infected cells -- these drugs help block HIV from getting inside healthy cells in the first place.	Enfuvirtide
Fixed-Dose Combinations	Some drug manufacturers put together specific medicines into a single pill so they're easier to take, including:	Integrase strand transfer inhibitor (INSTI)- based: Bictegravir + tenofovir alafenamide + emtricitabine, Dolutegravir + abacavir + lamivudine

1.2.4.1 HIV Medication Side Effects

Potential short-term side effects of antiretroviral therapy can include: diarrhea, difficulty sleeping, dizziness, fatigue, headache, muscle pain, nausea, vomiting.

Long-term side effects may include: depression, diabetes, heart disease, insomnia, kidney damage, liver damage, nerve damage, weak bones, (a condition that doctors call osteoporosis), higher levels of fat in the blood.[9] Jayne Leonard (2018)

1.2.5. Symptoms

HIV may not cause symptoms early on. People who do have symptoms may mistake them for the flu or mono. Common early symptoms include:

i. Fever.
ii. Sore throat.
iii. Headache.
iv. Muscle aches and joint pain.
v. Swollen glands (swollen lymph nodes).
vi. Skin rash.

Symptoms may appear from a few days to several weeks after a person is first infected. The early symptoms usually go away within 2 to 3 weeks.

After the early symptoms go away, an infected person may not have symptoms again for many years. After a certain point, symptoms reappear and then remain. These symptoms usually include:

i. Swollen lymph nodes.
ii. Extreme tiredness.
iii. Weight loss.
iv. Fever.
v. Night sweats.[10] Health Link BC (British Columbia), (2019)

1.2.6. Prevention

1.2.6.1. Mother-to-child transmission

Prevention of mother-to-child transmission has seen advances in both industrialized and resource-constrained settings. Intrapartum transmission has been reduced by increasing access to interventions such as one dose of nevirapine to mother and newborn baby.[11] Ekouevi DK, *et al*.(2005).

Concerns about drug-resistant viral strains have led to several trials with combination treatments to reduce transmission during the intrapartum period. In some

settings, elective delivery by caesarean section can further reduce HIV-1 transmission during the intrapartum period, but the benefits of the intervention could be countered by post-partum sepsis and increasing maternal mortality.[12] Read JS and Newell MK. (2005).

Because HIV-1 can be transmitted by breastfeeding, replacement feeding is recommended in many settings. Poor access to clean running water precludes, however, the use of formula feeding underthese circumstances, and exclusive breastfeeding with abrupt weaning is one option for reducing transmission.[13] Rollins N, *et al*. (2004).

1.2.6.2. Sexual transmission

Reduction of heterosexual transmission is crucial for control of the epidemic in many parts of the world. Prevention is achieved through reduction in the number of discordant sexual acts or reduction of the probability of HIV-1 transmission in discordant sexual acts. The first can be achieved through abstinence and sex between concordantly seronegative individuals.[14] Duerr A, *et al*. (2005). Abstinence and lifelong monogamous relationships might not be adequate solutions for many people and therefore several interventions aimed at lowering the risk of transmission per discordant sexual act are in the process of clinical testing. Male and female condoms provide a proven and affordable prevention option. In combination, these options are also more commonly referred to as the ABC (abstinence, be faithful, condom use) approach.[15] Tuomala RE, *et al*. (2002)

1.2.6.3. Microbicides

Microbicides are an additional important biomedical intervention technology that is covert and under women's control. These topical products potentially could be used to prevent rectal and vaginal transmission of HIV-1, but proof of concept has been elusive. Although the three phase III trial results of the first microbicidal product (nonoxynol-9) done in the mid-1980s and 1990s did not show protective effects, they have informed the medical knowledge in terms of product selection, clinical testing, and safety assessments. The past 5 years have seen major advances in investment and product development.[16] De Vincenzi I. (1994).

1.3. Anti-HIV/Anti-retroviral Drug

These are drugs active against human immunodeficiency virus (HIV) which is a retrovirus. They are useful in prolonging and improving the quality of life and postponing complications of acquired immunodeficiency syndrome (AIDS) or AIDS related complex (ARC), but do not cure the infection. The clinical efficacy of antiretrovirus drugs is monitored primarily by plasma HIV -RNA assays and CD4 lymphocyte count carried out at regular intervals. (Fig. 1.2)[17] Arts EJ and Hazuda DJ. (2012).

1.3.1. Pharmacological Targets for Antiretroviral Drugs

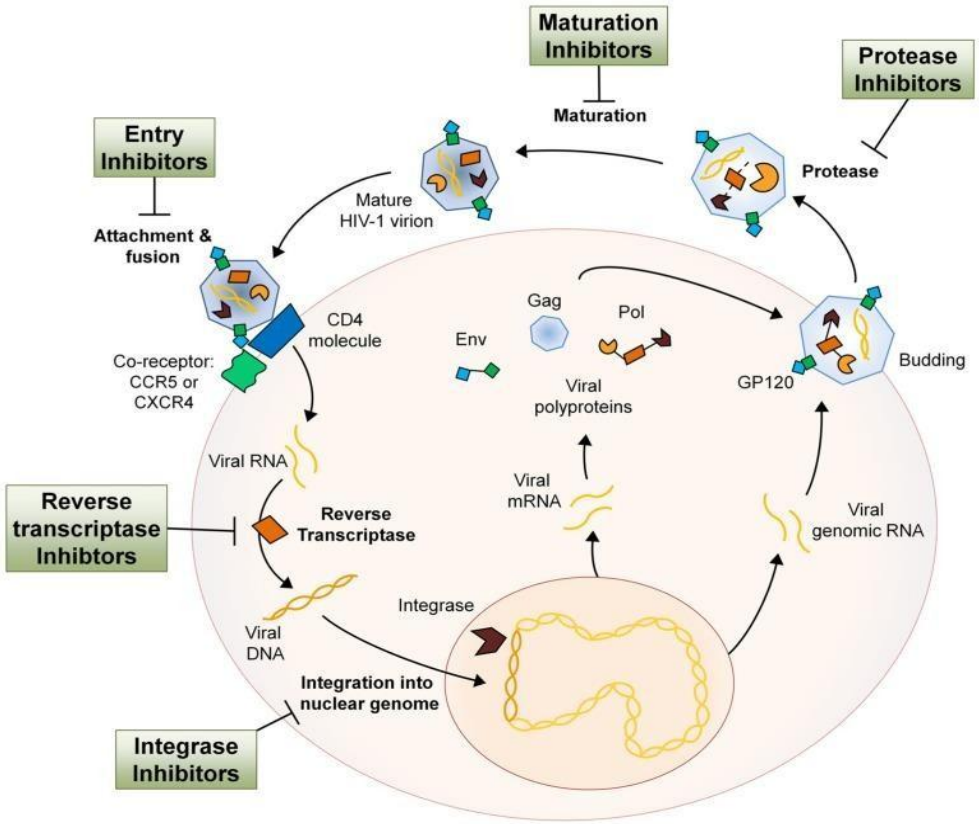

Figure 1.2: The-HIV-1-life cycle and-the antiretroviral drug-class intervention point's entry.

1.3.2. History of Anti-retroviral drug

Treatment of HIV has a long and rich history. In <30 years of antiretroviral therapy (ART), there have been more than 25 drugs developed (Fig. 1.3). In 1987, the first antiretroviral agent, zidovudine (AZT), a nucleoside reverse transcriptase inhibitor (NRTI), was shown to have a positive impact on clinical progression and death[18] Fisch MA, *et al.* (1987)

The challenges of early NRTI included high pill burdens, inconvenient dosing, treatment-limiting toxicities and incomplete virological suppression. Sequential monotherapy and incomplete virological suppression resulted in the emergence of multiple resistance mutations, with long-term treatment consequences. Human immunodeficiency virus (HIV) protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), introduced in the mid-1990s, revolutionized the management of HIV infection. Highly active antiretroviral therapy (HAART) regimens, consisting of two NRTIs plus a PI or NNRTI, were capable of virological suppression (<400 copies ml^{-1}), and widespread uptake quickly led to dramatic reductions in morbidity and mortality in the developed world[19] Palella FJ *et al.* (1998)

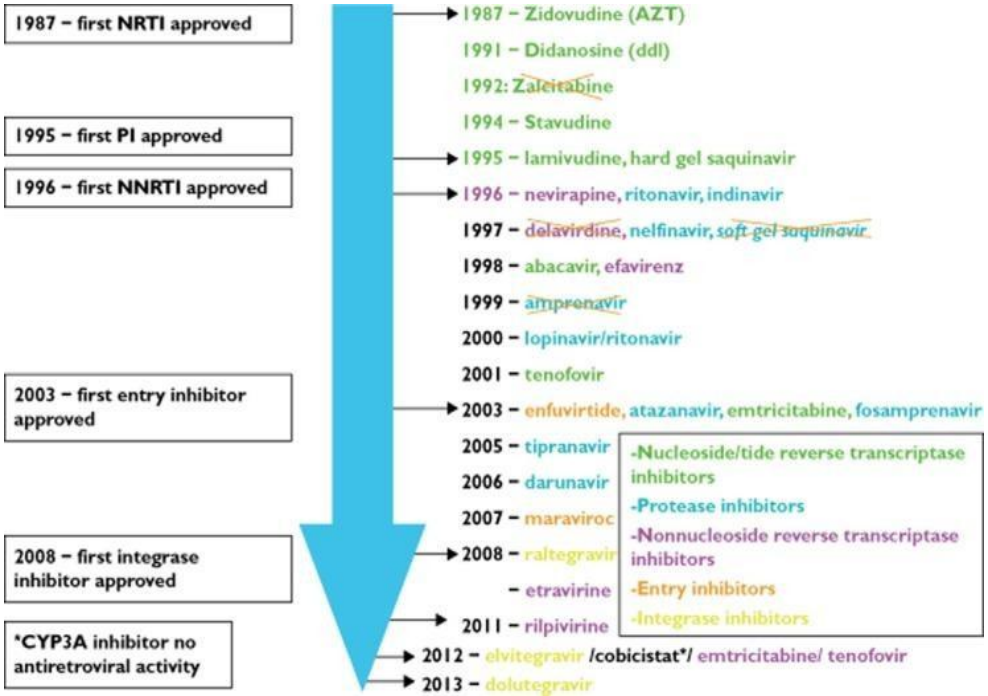

Figure 1.3: Time lines of antiretroviral development. The time course of development of >25 drugs across five different classes over the last 27 years is highlighted according to the US Food and Drug Administration (FDA) approval date. Those that are no longer in use or available are illustrated with an 'X' through them.

The strategy of using two NRTIs plus a potent third agent still forms the cornerstone of current treatment principles, and is now referred to as combination antiretroviral therapy. Combination- based ARV therapy (ART) was introduced in 1996, which led to effectively sustained HIV suppression, significantly recovered immune function, markedly improved clinical symptoms and notably extended lifespan. In the third decade, with further development of ARV drugs and the availability of multiple ART regimens and FDCs, acquired immune deficiency syndrome (AIDS) has become a chronic, manageable and infectious disease.[20] Ho DD. (1995).

A step forward occurred when the cytidine analog lamivudine (3TC) was developed. Whereas monotherapy was associated with the rapid development of resistance, the drug was synergistic with many of the other nucleosides including ZDV and was relatively well tolerated. In addition to combining lamivudine with ZDV, it was also given successfully with Stavudine (d4T) however, none of the dual nucleoside combinations, when administered without a third drug, could durably control HIV infection. Thymidine analogs were also progressively dismissed because of their toxicities.[21] Kuritzker DR, *et al.* (1999).

However, the most important result obtained with the initial use of NRTIs was the demonstration that the treatment of HIV-infected pregnant women substantially decreased HIV transmission to the newborn. Today, antiretroviral therapy to prevent mother-to-child transmission is based on triple drug combinations as the global standard, but single–double drug treatment was also used initially and represented an important proof of concept[22] Connor EM, *et al.* (1994)

1.3.3. Classification of Anti-retroviral drug

I. Nucleoside reverse transcriptase inhibitors (NRTIs): Zidovudine (AZT), Didanosine, Stavudine, Lamivudine, Abacavir, Emtricitabine, Tenofovir (Nt

RTI)

II. Nonnucleoside reverse transcriptase inhibitors (NNRTIs): Nevirapine, Efavirenz, Delavirdine
III. Protease inhibitors: Ritonavir, Atazanavir, Indinavir, Nelfinavir, Saquinavir, Amprenavir,Lopinavir
IV. Entry (Fusion) inhibitor: Enfuvirtide
V. CCR5 receptor inhibitor: Maraviroc
VI. Integrase inhibitor: Raltegravir[23] Tripathi KD, seventh ed. (2013).

1.3.3.1. Nucleoside Reverse Transcriptase Inhibitors

NRTIs were the first class of drugs to be approved by the FDA. NRTIs are administered as prodrugs, which require host cell entry and phosphorylation by cellular kinases before enacting anantiviral effect.

Lack of a 3′-hydroxyl group at the sugar (2′-deoxyribosyl) moiety of the NRTIs prevents the formation of a 3′-5′-phosphodiester bond between the NRTIs and incoming 5′-nucleoside triphosphates, resulting in termination of the growing viral DNA chain. Chain termination can occur during RNA-dependent DNA or DNA-dependent DNA synthesis, inhibiting production of either the (−) or (+) strands of the HIV-1 proviral DNA. Currently, there are eight FDA-approved NRTIs: abacavir (ABC, Ziagen), Didanosine (ddI, Videx), emtricitabine (FTC, Emtriva), lamivudine (3TC, Epivir), stavudine (d4T, Zerit), zalcitabine (ddC, Hivid), zidovudine (AZT, Retrovir), and Tenofovirdisoprovil fumarate (TDF, Viread), a nucleotide RT inhibitor (Fig. 1.4).[24] Hart, *et al*. (1992).

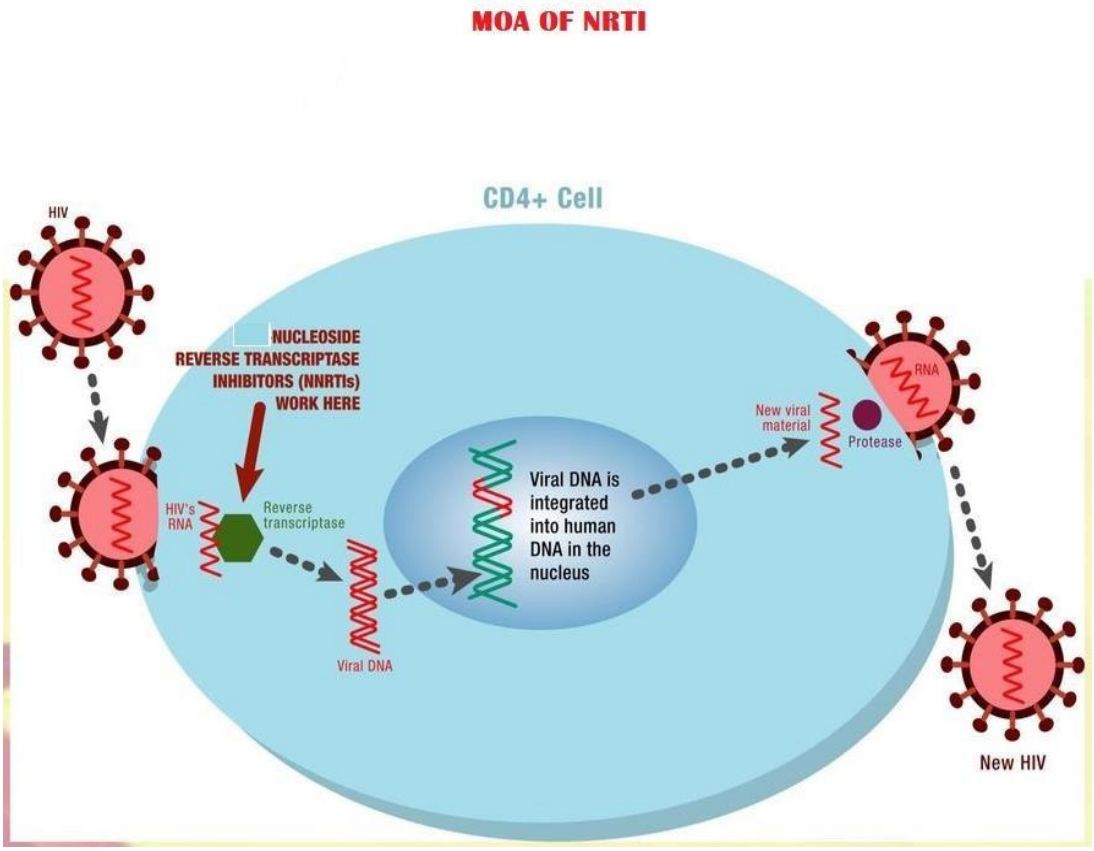

Figure 1.4: MOA of NRTI (Nucleoside Reverse Transcriptase).

Recently, the guidelines for the industrialized nations have been revised by the US Department of Health and Human Services (DHHS) where tenofovir (TDF) and emtricitabine (FTC) combination is the preferred NRTI component in an initial regimen. This combination has shown superior virologic and immunologic response as compared to AZT + 3TC and is also effective against hepatitis B virus with lower rate of lipotrophy as compared to stavudine and AZT.[25] Santos SA, *et al.* (2006).

Although nephrotoxicity has been a concern with TDF, it is rare in treatment-naive patients but requires a periodic monitoring of renal function. Even abacavir (ABC) has been stepped down to alternative option on an initial therapy due to reports of high virologic failure, hypersensitivity and cardiovascular risk, especially myocardial infarction. The new agent's apricitabine and elvucitabine are currently being evaluated against HIV-1 isolates resistant to conventional NRTIs.[26] El Safadi Y, *et al*. (2007).

1.3.3.2. Non–Nucleoside Reverse Transcriptase Inhibitors

NNRTIs inhibit HIV-1 RT by binding and inducing the formation of a hydrophobic pocket proximal to, but not overlapping the active site (Fig. 1.5). The binding of NNRTIs changes the spatial conformation of the

substrate-binding site and reduces polymerase activity[27] Spence, *etal*. (1995).

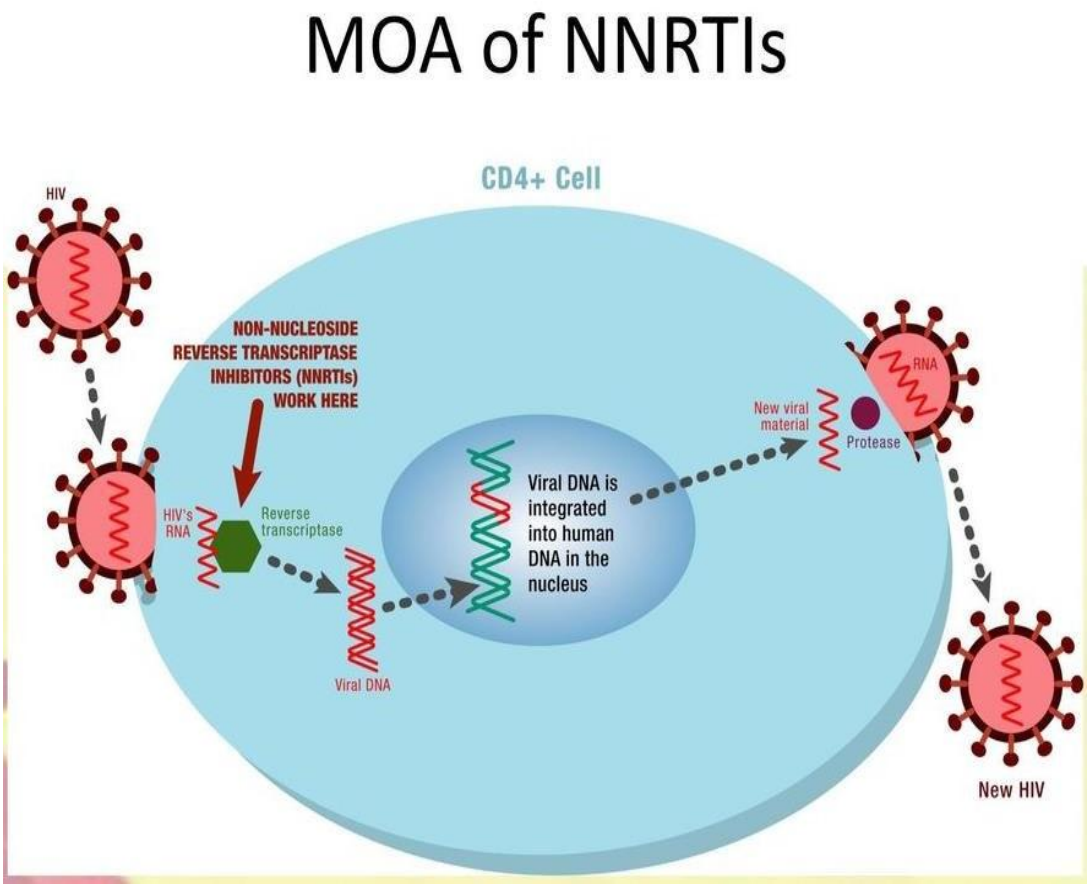

Figure 1.5: MOA of NNRTI (Non-Nucleoside Reverse Transcriptase).

The NNRTI-binding pocket only exists in the presence of NNRTIs and consists of hydrophobic residues (Y181, Y188, F227, W229, and Y232), and hydrophilic residues such as K101, K103, S105, D192, and E224 of the p66 subunit and E138 of the p51 subunit. Unlike NRTIs, these non/uncompetitive inhibitors do not inhibit the RT of other lentiviruses such as HIV-2 and simian immunodeficiency virus (SIV). Currently, there are four approved NNRTIs: etravirine, delavirdine, efavirenz, and nevirapine, and several in development, including rilpivirine in phase.

3. [28]Witvrouw, *et al*. (1999)

1.3.3.3. PROTEASE INHIBITORS

The HIV-1 protease is the enzyme responsible for the cleavage of the viral gag and gag-pol polyprotein precursors during virion maturation Miller. 10 PIs are currently approved: amprenavir (APV, Agenerase), atazanavir (ATZ, Reyataz), darunavir (TMC114, Prezista), fosamprenavir (Lexiva), indinavir (IDV, Crixivan), Lopinavir (LPV), nelfinavir (NFV, Viracept), ritonavir (RTV, Norvir), saquinavir (SQV, Fortovase/Invirase), and tipranavir (TPV, Aptivus) (Fig. 1.6).

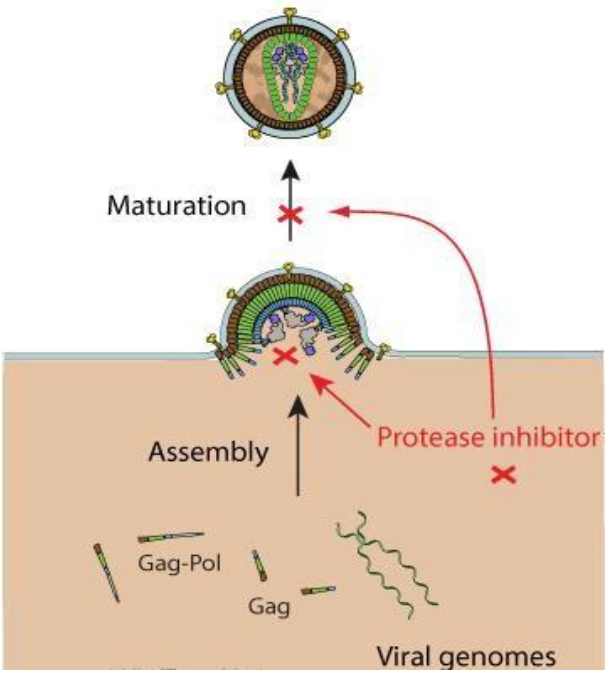

Figure 1.6: MOA of Protease Inhibition.

Because of its vital role in the life cycle of HIV-1 and relatively small size (11 kDa), it was initially expected

that resistance to protease inhibitors would be rare. However, the protease gene has great plasticity, with polymorphisms observed in 49 of the 99 codons, and more than 20 substitutions known to be associated with resistance.[29] Shafer, *et al*. (2000).

1.3.3.4. Entry Inhibitors

HIV-1 entry exploits several host proteins for a set of intricate events leading to membrane fusion and virus core release into the cytoplasm. HIV-1 entry inhibitors can be subdivided into distinct classes based on disruption/inhibition of distinct targets/steps in the process.

1.3.3.4.1. Fusion Inhibitors

The crystal structure of the gp41 ectodomain and of the ectodomain partnered with an inhibitory peptide (C34) revealed that the fusion-active conformation of gp41 was a six-helix bundle in whichthree N helices form an interior, trimeric coiled coil onto which three antiparallel C helices pack.[30] Doms and Wilen (2011).

Peptide fusion inhibitors were designed based on the discovery that two homologous domains in the viral gp41 protein must interact with each other to promote fusion, and that mimicry of one of these domains by a heterologous protein can bind and disrupt the intramolecular interactions of the virus protein. Alpha-helical peptides homologous to the leucine zipper domain of gp41 had significant antiviral activity against HIV-1, and this activity depended on their ordered solution structure. Rational design of helical inhibitors ultimately produced a molecule (T-20, enfuvirtide) with potent antiviral activity in vivo (Fig. 1.7)[31] Lalezari, *et al*. (2003).

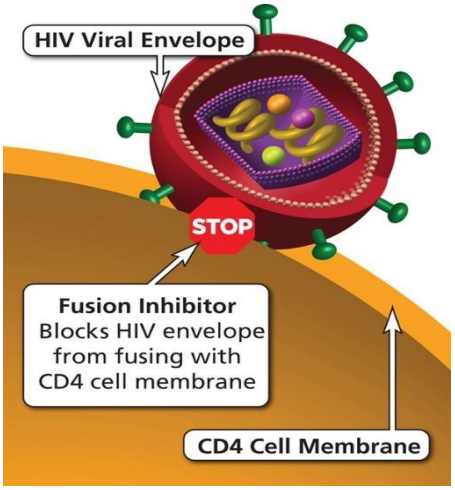

Figure 1.7: MOA of Entry (Fusion) Inhibitor.

1.3.3.5. INTEGRASE INHIBITORS

Integrase was the most recent HIV-1 enzyme to be successfully targeted for drug development. Raltegravir (RAL), MK-0518 was FDA approved in 2007, and other integrase inhibitors, including Elvitegravir (EVG), GS-9137 are progressing through clinical development. As mentioned above, integrase catalyzes 3′ end processing and viral DNA and strand transfer. All integrase inhibitors in development target the strand transfer reaction and are thus referred to as either INIs or more specifically, integrase strand transfer inhibitors (InSTIs).[32] McColl and Chen (2010).

The selective effect on strand transfer is a result of a now well-defined mechanism of action in which the inhibitor (1) binds only to the specific complex between integrase and the viral DNA and (2) interacts with the two essential magnesium metal ion cofactors in the integrase active siteand also the DNA (Fig. 1.8).

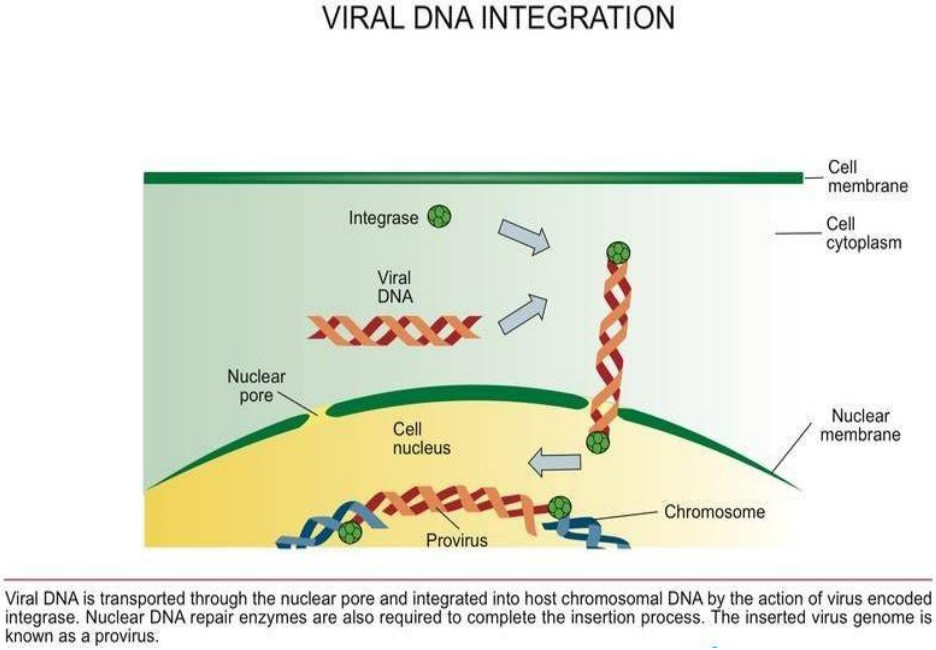

Figure 1.8: MOA of Integrase Inhibitor.

Therefore, all InSTIs are comprised of two essential components: a metal-binding pharmacophore, which sequesters the active site magnesium, and a hydrophobic group, which interacts with the viral DNA as well as the enzyme in the complex. InSTIs are therefore the only ARV class that interacts with two essential elements of the virus, the integrase enzyme as well as the viral DNA, which is the substrate for integration.[33] Grobler, et al. (2002).

1.3.3.6. Small-Molecule CCR5 Antagonists

Small-molecule CCR5 antagonists bind to hydrophobic pockets within the transmembrane helicesof CCR5. This site does not overlap the binding sites of either CCR5 agonists or HIV-1 envelope. Instead, drug binding induces and stabilizes a receptor conformation that is not recognized by either. Thus, these molecules are considered allosteric inhibitors. Ideally, a small-molecule inhibitor of CCR5 would block binding by HIV-1 envelope but continue to bind native chemokines and allow signal transduction. Most small-molecule inhibitors, however, are pure antagonists of the receptor. Oral administration of small-molecule antagonists has been shown to inhibit viral replication in macaque models and to prevent vaginal transmission. Thus far, three antagonists (VCV, MVC, and Aplaviroc) have been shown to inhibit virus replication in humans. The compound MVC was approved for therapeutic use by the FDA in 2007 (Fig. 1.9).[34] Veazeyet,*et al*. (2005).

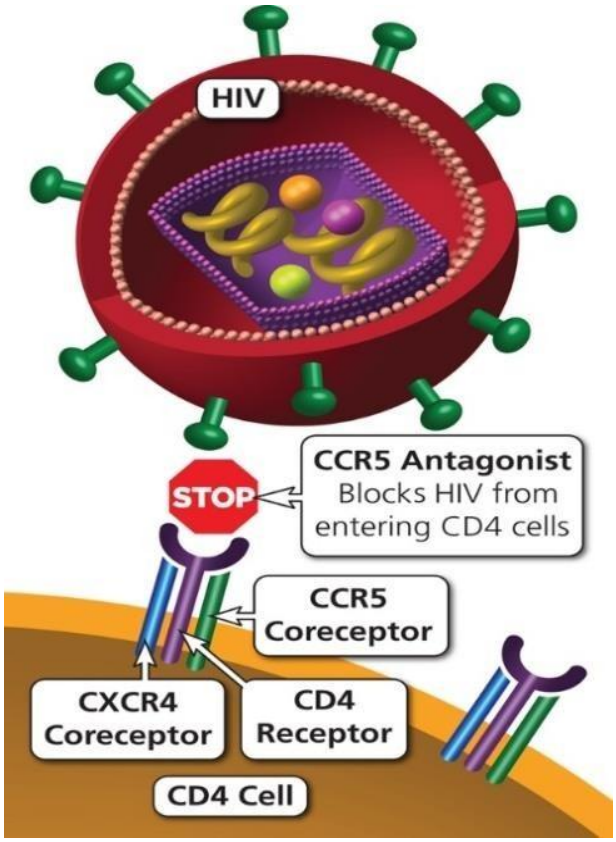

Figure 1.9: MOA of CCR5 Antagonist.

2.1. Literature Review

The past, present, and future of antiretrovirals (ARVs) for the treatment and prevention of HIV infection are summarised in this study. The development of novel antiretroviral (ARV) medications has stagnated, despite substantial research into the efficacy and safety of once-daily fixed dose combinations. Several classic antiretroviral medicines are still in phase III testing. This study also highlights existing ARV drug information and focuses on ARV drug development in the coming decade.

2.1.1.1. Anti-retroviral drugs approved by FDA

The first AIDS cases were reported in 1981 in nited States. The human immunodeficiency virus (HIV) was defined as etiologic microorganism in 1983. Just four years later, the first HIV medicine Zidovudine was approved by US FDA and quicklyopened the new era for anti-retroviral chemotherapy. In the following thirty to forty years,the FDA approved a total of 58 anti-retroviral drugs including 34 single-tablets and 24 FDCs therapeutics. These agents are classified into eight categories of ARV drugs: nucleoside reversetranscriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), fusion inhibitors (FIs), entry inhibitors (EIs), pharmacokinetic enhancers (PEs) and fixed- dose combinations (FDCs) Fig 2.1.[35] Kiyota T, *et al.* (2015).

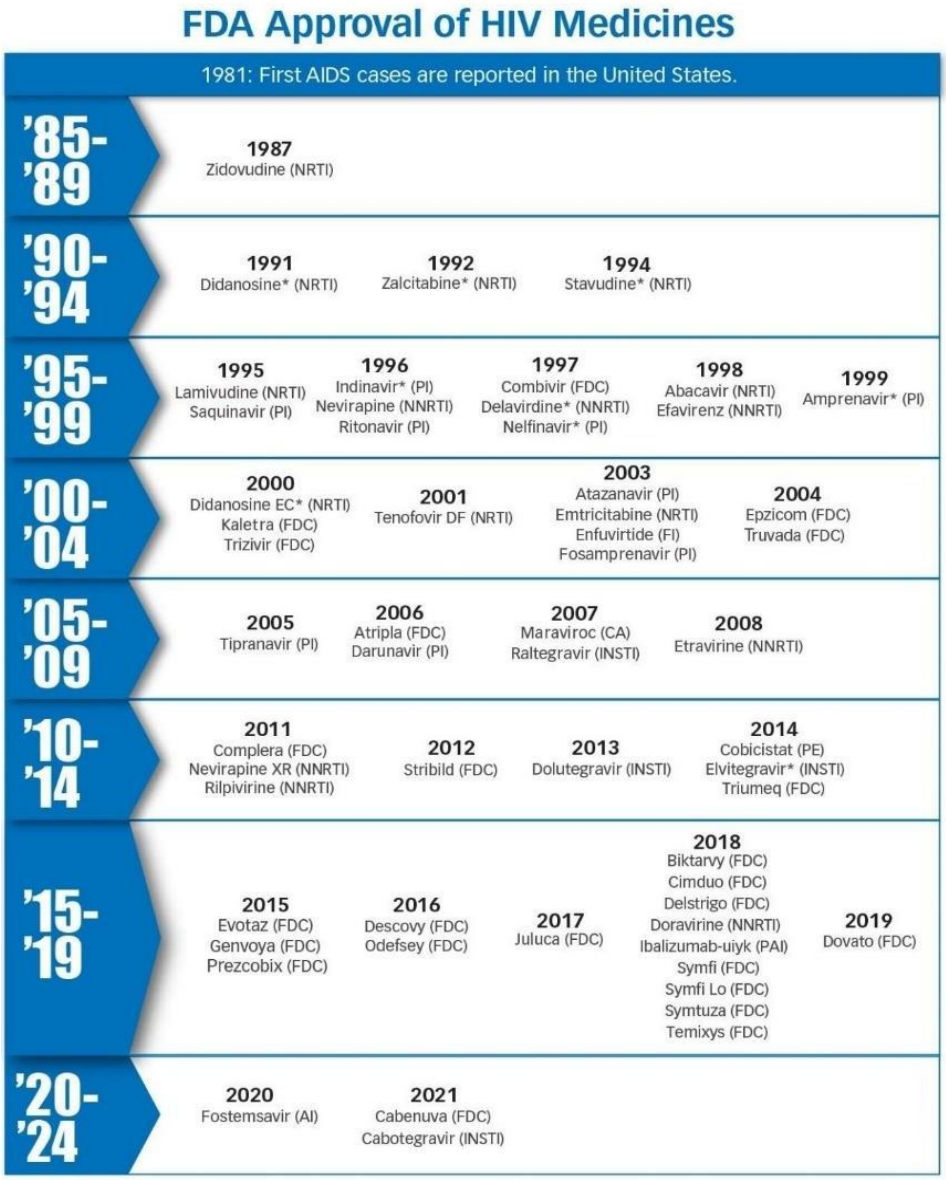

Figure 2.1: FDA Approval of HIV Medicines.

2.1.1.2. Current State of Anti-retroviral Drug

The US Food and Drug Administration (US FDA) had approved 58 antiretroviral medicines for clinical use by the end of 2021, including 34 single-tablets and 24 fixed-dose combos (FDCs). The intensity of the search for novel antiretroviral (ARV) compounds has slowed during the last 10 years while some classic agents are still in phase III clinical trials. Long-acting formulations, oral attachment inhibitors, maturation inhibitors, and novel approaches to cure the illness will be prioritised in the development of new anti-HIV-1 medications during the next decade to increase treatment safety, adherence, and efficacy.[36] Xingquan Zhang, (2021).

However, there are many challenges that remain. While many of the newer agents are tolerable, long term side effects (e.g. metabolic and cardiovascular) and drug-drug interactions remain a concern. Patients faced with the need to take "lifelong" therapy for upwards of fifty years require agents with safer long term side effects. The approval of tenofoviralafenamide will likely reduce the incidence of bone and renal toxicity; however, long term data over a lifetime is needed to guide therapy. While there are many treatment options available to decrease HIV RNA, an agent to increase CD4 T-lymphocyte count remains elusive.[37] De Claeracq, (2017).

Many programs are in place to close the gap between access in developed and non-developed countries. The current WHO guidelines recommend that all patients are started on ARV therapy regardless of CD4 T-lymphocyte count. The scale up of these programs requires the funding and infrastructure to treat a larger number of patients.[38] World Health Organization, (2018).

As tolerability of medications is no longer a main concern, the conversation has shifted to medication adherence and engagement in care. The "HIV Cascade" has many steps for which intervention and research are required. Engagement and continuation of ARV therapy

after transitions in care remains an issue. The transitions from adolescent to adult and prison to society each have their own unique challenges.[39] Wohl DA, *et al.* (2017).

2.1.2. Challenges with the Use of ARV Drugs

The critical issues associated with ART are related to the characteristic features of the virus (HIV), ARV drugs and HIV positive patients. These factors are a major challenge for an effective long term treatment.[40] Williams KJ & Loeb LA (1992).

2.1.2.1. HIV related factors

1. HIV, a retrovirus, multiplies at a rate of approximately 10^{10} copies per day. At such a high rate of replication, the virus often commits mistakes and results into mutants. High mutation rate leads to development of multiple strains and threatens the development of drug resistance.
2. Once infected, the virus becomes an integral part of host cell and survives the full life span of infected host cell, especially in T-lymphocytes and urogenital secretions. Surprisingly, despite a complete plasma viral load suppression for 6-12 months, the virus remains detectable in seminal fluid and more often than not, these are drug resistant variants. The existence of virus in potential 'reservoirs' and the subsequent replication may cause relapse following cessation of ART, necessitating lifelong treatment. Different treatment strategieshave been tried for the persistent forms, but to date, no clinical or virological benefit has been reported.
3. Increasing reports of multi-drug resistant (MDR) virus in treatment-experienced patients are also being encountered.[41] Martinez-Cajal JL & Weinberg MA, (2008)

2.1.2.2. ARV related factors

1. Attempts to eradicate the virus from the 'reservoir' have failed despite intensifying the ARV treatment, implying that drugs cannot reach in adequate concentration in the latent reservoir cells.
2. Each class of ARV drugs has the potential to cause toxicities, many of which are shared by drugs likely to be used concomitantly in HIV positive patients. This complicates the treatment, causes difficulty in causality assessment and may require treatment withdrawalin serious life threatening reactions. Long term use of HAART has been reported to produce morphologic and metabolic abnormality syndrome, especially hypertriglyceridemia (HTG). This in turn has increased the risk of cardiovascular (CVS) and cerebrovascular diseases in patients receiving ART.[42] Carr A, *et al*. (1998).
3. Clinically significant drug-drug interactions, frequently seen in patients on ART, can adversely affect the patient care and complicate ART. Interactions have been observed in 14% to 26% of HIV infected patients in USA and Netherlands. The therapeutic risk of interactions is due to potent induction or inhibition of cytochrome P450 (CYP450) isoenzyme, which also metabolizes a number of other medications.[43] Ladenheim D, *et al*. (2008)
4. The limited availability of ARV drugs and safe alternatives in resource poor countries further add to the problem. The lack of monitoring for adverse events and poor access to therapeutic drug monitoring facilities also interfere with effective ART management.[44] Johnson VA, *et al*. (2008)

2.1.2.3. Host related factors

1. He success of HAART has increased the life expectancy of HIV patients. This has resulted into increased number of patients over 50 years, living with HIV. It is likely that these elderly patients are exposed to broad range of concomitant medications along with ARV regimens. However, the choice of these medications may not be always straightforward. The metabolic side effects of these ART increase the risk of CVS disease. The selection of antihypertensive and antihyperlipidemic agents need extra care, and the most appropriate drug may not always be a first line agent.[45] Nguyen N & Holodniy M, (2008)
2. A pre-treatment counseling of patient and family members regarding the disease, strict adherence to drug treatment, regular follow-up, changing the life style and dietary measures are essential elements for successful treatment. All these require deep understanding and co-operation from HIV patients that may be challenging in developing countries.[46] Bozzette SA, *et al*. (2003)

2.1.3. Recent Advancement

2.1.3.1. Pharmacokinetic enhancers: The current strategy is to exploit the pharmacokinetic profile of one ARV drug to enhance the therapeutic effect of the concomitant ARV drug. This has opened the possibility of pharmacokinetic enhancers without having anti-HIV activity. Ritonavir is already being used extensively to boost other PIs. Surprisingly, it has been observed that ritonavir can also boost drugs in other classes such as, elvitegravir (an integrase inhibitor) and vicriviroc (a CCR5 inhibitor). However, ritonavir is associated with gastrointestinal intolerance, dyslipidemia and diabetes. Pharmacokinetic enhancers are a major step towards identifying ritonavir alternatives.[47] Mathias AA, *et al.* (2010).

2.1.3.1.1. Cobicistat (GS-9350), SPI-452

Cobicistat and SPI-452 are 2 compounds under investigation. Cobicistat has no anti-HIV activitybut is a potent inhibitor of CYP3A. It increases the blood level of certain ARV drugs, allowing once-daily dosing. It is found to be safe and well-tolerated in escalating single and multiple dose-ranging studies in healthy volunteers. It is under trial as a standalone boosting agent for PIs, especially atazanavir and integrase inhibitor elvitegravir as FDC and found to be comparable withritonavir. It also has a low potential to cause lipid and glucose

abnormalities than ritonavir. SPI- 452 is another investigational pharmacokinetic enhancer without anti-HIV activity. It is being investigated to increase the exposure of darunavir and atazanavir. Both the drugs have been shownto enhance the plasma levels of PIs.[48] Cohen C, *et al.* (2010)

2.1.3.2. CD4 receptor attachment inhibitors

The attachment of outer membrane gp120 to CD4 receptor is inhibited by investigational compounds that constitute the new class of CD4 receptor attachment inhibitors.

2.1.3.2.1. Ibalizumab (TNX-355)

Ibalizumab, a humanized monoclonal IgG4 antibody against CD4 receptors, was granted fast track status by US-FDA in 2003. It inhibits viral entry by attaching with extracellular domain of CD4 receptors. The binding site is distinct from gp120 and is designed in a way so as not to interfere with immunological function of CD4 receptors. Its novel mechanism of action leads to potent antiviral activity in spite of HIV tropism and an unlikely cross-resistance with other antiretrovirals. A single dose, proof of concept study showed efficacy and tolerability of a range of doses (0.3 mg/kg to 2 5 mg/kg). The greatest effect in reducing viral load and increase in CD4 count is seen at 25 mg/kg. Adverse effects have been observed to be headache, rashes, nasal congestion and urticarial. Similar efficacy was also seen in phase Ib study with once and twice a week regimens. A phase Ib study was found to decrease the HIV-RNA copy initially for 2 weeks, however, the levels increased back towards baseline, indicating reduced susceptibility. It has also shown synergistic effect with fusion inhibitors. Parenteral administration of the agent may be a problem for regular use. The drug is under further evaluation.[49] Jacobson JM, *et al*. (2009)

2.1.3.3. HIV maturation inhibitors: This is an emerging class of drugs that targets internal structural protein precursor Gag, which is vital in final stage of virus development for a mature and infectious virion.

2.1.3.3.1. Bevirimat (formerly PA-457): Bevirimat is a novel agent that acts on the last and important stage of HIV maturation before it buds from host cell. The primary target of the drug is gag polyprotein precursor, the main structural protein of the assembly and budding of the viral particles. It prevents the cleavage of the precursor protein to a mature viral capsid protein. This disrupts gag processing and results in defective, immature, non-infectious viral particle. The pharmacokinetic profile is favorable with long half-life and once a day dosing. A preliminary phase II-b trial in patients with resistance to 3 antiretroviral drug classes has shown decline in plasma HIV-RNA level. The initial results are encouraging, and it seems that maturation inhibitors may find a place in HIV therapeutics in coming years. Bevirimat has been granted the fast track statusby the FDA in 2005.[50] Salzwedel K, *et al*. (2007).

2.1.3.4. Lens epithelium derived growth factor inhibitor: HIV-1 can integrate their DNA at different sites in host DNA. During the pre-integration complex, the HIV integrase interacts and binds with host cell factors. Researchers have identified lens epithelium derived growth factor (LEDGF) that directs HIV-1 DNA integration to different sites in host genome. This interaction has been an interesting target for antiviral therapy. Researchers used rational design to identify small molecules to fit the interaction by a series of 2 - (quinoline-3-yl) acetic acid derivatives. These compounds have been investigated as lens epithelium derived growth factor inhibitor. It hasbeen observed that CX00287 moderately inhibits LEDGF and HIV replication in vitro. Further research is going on.[51] Christ F, *et al*. (2010).

2.1.3.5. Capsid assembly inhibitors: Capsid assembly inhibitors are a new class of drugs for treating HIV infection. Virus capsid is made up of identical, symmetrically arranged protein blocks that maintain the structure of the virus particle. It plays an important role in early and late stages of viral replication and is essential for the survival and infectivity of the virus. Hence, virus capsidhas been recognized as a potential target for new class of ARV drugs. The molecule that inhibits the interactions between structural proteins would affect the integrity and survival of the virus.

2.1.3.5.1. PF-3450071 and PF-3450074: PF-3450071 and PF-3450074 act early in the HIV-1 replication cycle at a step following HIV-1 envelope-mediated entry. Both the compounds were evaluated in single cycle infection assays and in the viral production-infectivity assay, using NFV (PI) and EFV (NNRTI) as late stage and early stage inhibitor controls. Both of them inhibited the production of infectious virus.[52] Blair WS, *et al*. (2010)

2.1.4. Future Promises

Given the high efficacy, safety, tolerability, and convenience of contemporary ARV therapy, it can be challenging to identify where and to what extent improvements can be made. However, considering the vast advancements in treatment that have already occurred, it may be naive to think that the current approach to HIV treatment is the best and only way.

New agents under investigation are challenging the current treatment paradigm of three active antiretroviral medications by mouth every day to maintain viral suppression. Several two drug therapy options are emerging that may simplify treatment and reduce cost. Long-acting medications dosed every week or every month may be easier for some patients, improve medication adherence, and increase cost effectiveness.[53] Pons-Faudoa FP, *et al*. (2020).

The last component of the treatment paradigm, the consistent need for antiretroviral medications, may be the most challenging of all to change. Will broadly

neutralizing antibodies, therapeutic vaccines, latency reversing agents, or CRISPR technology ever become routine methods for inhibiting, suppressing, or eliminating HIV. Evidence for these approaches and others continue to emerge and provide optimism that the future may hold a potential cure.[54] Yin C, *et al.* (2017).

3.1. CONCLUSION

Treatment for HIV has progressed from arduous regimens with high pill burdens, inconvenient dosing, treatment-limiting toxicities, food and drug interactions, incomplete viral suppression, and the emergence of drug resistance to manageable one- or two-pill once-daily regimens that can be started in early HIV disease and continued with viral replication control for much of a person's lifespan. Those who have regained their immune system and are still virologically suppressed should have a normal life expectancy.

Advances in pharmacology in the investigation and treatment of HIV have been at the cutting edge of science. Pharmacogenomics discovery and translation (HLA-B&57:01 screening to prevent abacavir hypersensitivity), drug class and formulation discovery (fixed-dose combination, long- acting injectable nano-formulations), pharmacokinetic enhancement, and management and decision support for complex drug–drug and food–drug interactions are just a few examples. The science and translation of HIV eradication strategies, as well as continued globalisation of ART through scale-up and continued improvements in cost efficiency, engagement and retention of patients in care, new immunological and pharmacological approaches to prevention, and new immunological and pharmacological approaches to prevention, and new immunological and pharmacological approaches to prevention, are all current and future challenges.

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