

## CURRENT TREATMENT OF HIV INFECTION A REVIEW SIMPLIFIED: AN UNDERSTANDING ABOUT HIV INFECTION AND ANTI HIV DRUGS MECHANISAM OF ACTION

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### ABSTRACT

Virtually all the compounds that are currently used, or under advanced clinical trial, for the treatment of HIV infections, belong to one of the following classes: (i) nucleoside reverse transcriptase inhibitors (NRTIs): i.e. zidovudine, didanosine, zalcitabine, etc. (ii) non-nucleoside reverse transcriptase inhibitors (NNRTIs): i.e. nevirapine, delavirdine, etc. (iii) protease inhibitors (PIs): i.e. saquinavir, ritonavir, etc. In addition, various other events in the HIV replicative cycle are potential targets for chemotherapeutic intervention: (i) viral adsorption, through binding to the viral envelope glycoprotein gp120; (ii) viral entry, through blockade of the viral coreceptors CXCR4 and CCR5; (iii) virus-cell fusion; (iv) viral assembly and disassembly; (v) proviral DNA integration; (vi) viral mRNA transcription. Also, new NRTIs, NNRTIs and PIs have been developed that possess respectively improved metabolic characteristics, or increased activity against Anti-HIV-resistant HIV strains.

**Keywords:** HIV Infection, Anti HIV drug mechanism.

### INTRODUCTION <sup>1</sup>

Viruses are small infectious agents consisting essentially of nucleic acid (either RNA or DNA) enclosed in a protein coat or capsid.

The coat plus the nucleic acid core is termed as the nucleocapsid. Some viruses have, in addition, a lipoprotein envelope, which may

contain antigenic viral glycoproteins, as well as host phospholipids acquired when the virus nucleocapsid buds through the nuclear membrane or plasma membrane of the host cell.

Certain viruses also contain enzymes that initiate their replication in the host cell. The whole infective particle is termed as a virion. In different types of viruses the genome may be or single stranded.

### Worldwide ratio of HIV infection

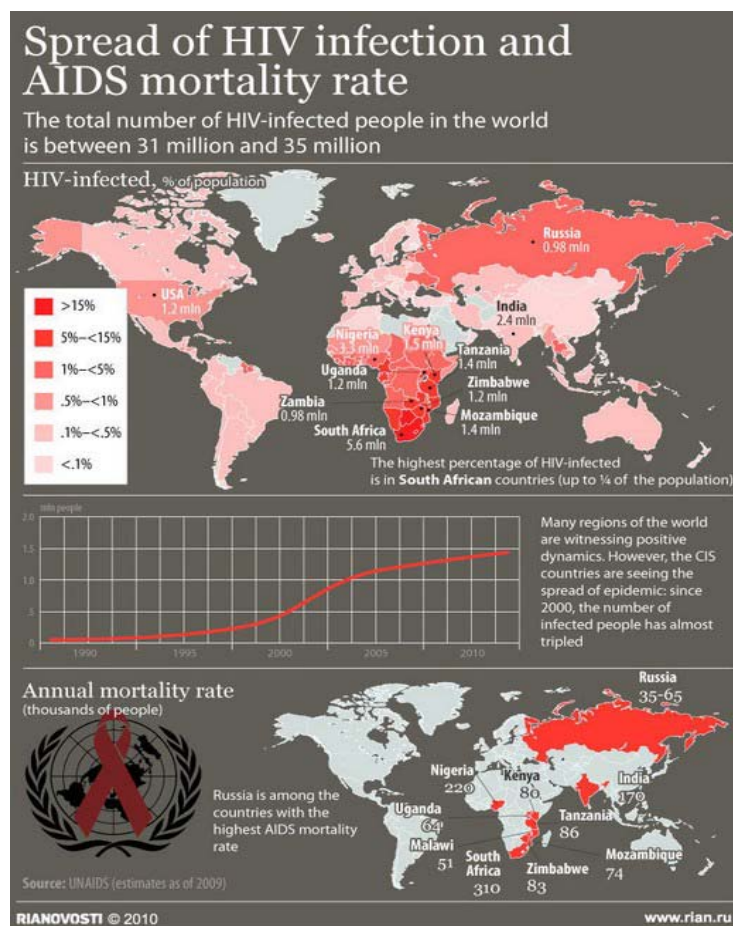


Fig. 1: Worldwide ratio of HIV infection <sup>6</sup>

### Replication in retroviruses

The virion in retroviruses contains a reverse transcriptase (virus RNA-dependent DNA polymerase), which makes a DNA copy of the viral RNA.

This DNA copy is integrated into the genome of the host cell and it is then termed a *provirus*.

The proviral DNA is transcribed into both new genomic RNA and mRNA for translation into viral proteins. The completed viruses are released by budding and many can replicate without killing the host cell.

The Human Immunodeficiency Virus<sup>4</sup> is responsible for Acquired Immuno Deficiency Syndrome (AIDS). HIV was discovered in 1983 by Luc Montagnier at the Pasteur Institute in France. The HIV-1 is the primary cause of AIDS, a slow, progressive and degenerative disease of the human immune system. AIDS is also defined by numerous opportunistic infections and cancers that occur in the presence of HIV infection. Forty million people are infected globally. It is the fourth most common cause of death worldwide. Thirty three percent of the cases are less than 24 years of age.<sup>5</sup> The disease has killed more than 21.8 million men, women and children worldwide.

### HIV infection and its pathological effects

#### Mode of viral transmission

- Unprotected sex
- Sharing of hypodermic needles for injections for drug use
- From HIV infected mother to the baby
- Human breast milk
- Blood transfusion and coagulation product.

#### Cellular picture of the infection <sup>10</sup>

Once the virus is inside the body, it targets a certain type of cell called T4-lymphocyte, a white blood cell that has a central role in regulating the immune system, specifically the CD-4 helper T-cell.

The virus then bursts into action, reproducing itself so furiously that the new viral particles escaping from the cell riddle the cellular membrane with holes and the lymphocyte ultimately dies.

HIV starts its replication cycle in the host cell with the help of the enzyme *Reverse Transcriptase*. The enzyme uses viral RNA as a template to assemble a double strand of viral DNA. The latter travels to the cell nucleus and inserts itself among the host chromosome, which provides the machinery for HIV-1 transcription and translation.

### Clinical picture of HIV infection

#### Immunosuppressive effect <sup>11</sup>

The hallmark of AIDS is a fall from a normal value of 800-1300 cells/cm<sup>2</sup> of blood to below 200 which may give threatening illness.

The suppressed immune system leaves the patient vulnerable to the so-called opportunistic infections by agents that would not harm a healthy person. The most common of such infections is pneumonia caused by *Pneumocystis carinii*.

Most of the clinical complications of AIDS patients result from such infections.

#### Neurological effects

The chief pathologies observed in the brain which appears to be independent of the immunodeficiency are an abnormal proliferation of the glial cells that surround the neurons and lesions resulting from loss of white matter.

This can ultimately give rise to a wide range of neurological symptoms such as dementia and multiple sclerosis.

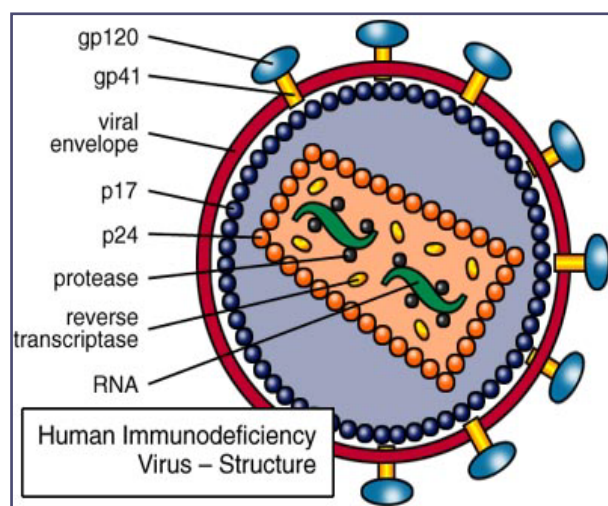
#### Carcinogenic effects

Cancer is the third main type of HIV induced pathological manifestations. People infected with the virus have an increased risk of at least three types of human tumors. One is known as *Kaposi's sarcoma* a rare tumor of blood vessel tissue in the skin or internal organs. The second type of cancer is *carcinoma* including skin cancer which is often seen in the mouth or rectum of infected homosexuals. The third major type of cancers observed with HIV infection are B-lymphomas (tumors originating in B-lymphocytes).

#### HIV structure and molecular biology <sup>12,13</sup>

##### HIV structure

The AIDS virus exists as a small particle called HIV virion. The particle is spherical in shape, with a diameter of roughly 1000Å units. It is around 60 times smaller than a red blood cell. The particle is covered by a membrane, made up of lipid (fatty) bilayer material known as the viral envelope (or membrane).

Fig. 2: Structure of HIV particle <sup>14</sup>

Projecting from this particles are around 72 little spikes, which are formed from the proteins gp120 and gp41. Just below the viral envelope is a layer called the matrix, which is made from the protein p17

The viral core (or capsid) is usually bullet-shaped and is made from the protein p24. Inside the core are three enzymes required for HIV replication called *reverse transcriptase*, *integrase* and *protease*. Also held within the core is HIV's genetic material, which consists of two identical strands of RNA.

The envelope glycoproteins have an important role in HIV entry to its host cell and also in the death of the host cell.

#### HIV genome <sup>15,16</sup>

HIV has several major genes encoding for structural proteins that are found in all retroviruses and several nonstructural ("accessory") genes that are unique to HIV. The *gag* gene provides the physical infrastructure of the virus; *pol* provides the basic enzymes by which retroviruses reproduce; the *env* gene supplies the proteins essential for viral attachment and entry into a target cell. The accessory proteins *tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu* enhance virus production. Although called accessory proteins, *tat* and *rev* are essential for viral replication.

In some strains of HIV, a mutation causes the production of alternate accessory protein, from the fusion of *tat*, *rev*, and *env*. The gp120 and

gp41 proteins, both encoded by the *env* gene, enable the virus to attach to and fuse with target cells to initiate the infectious cycle.

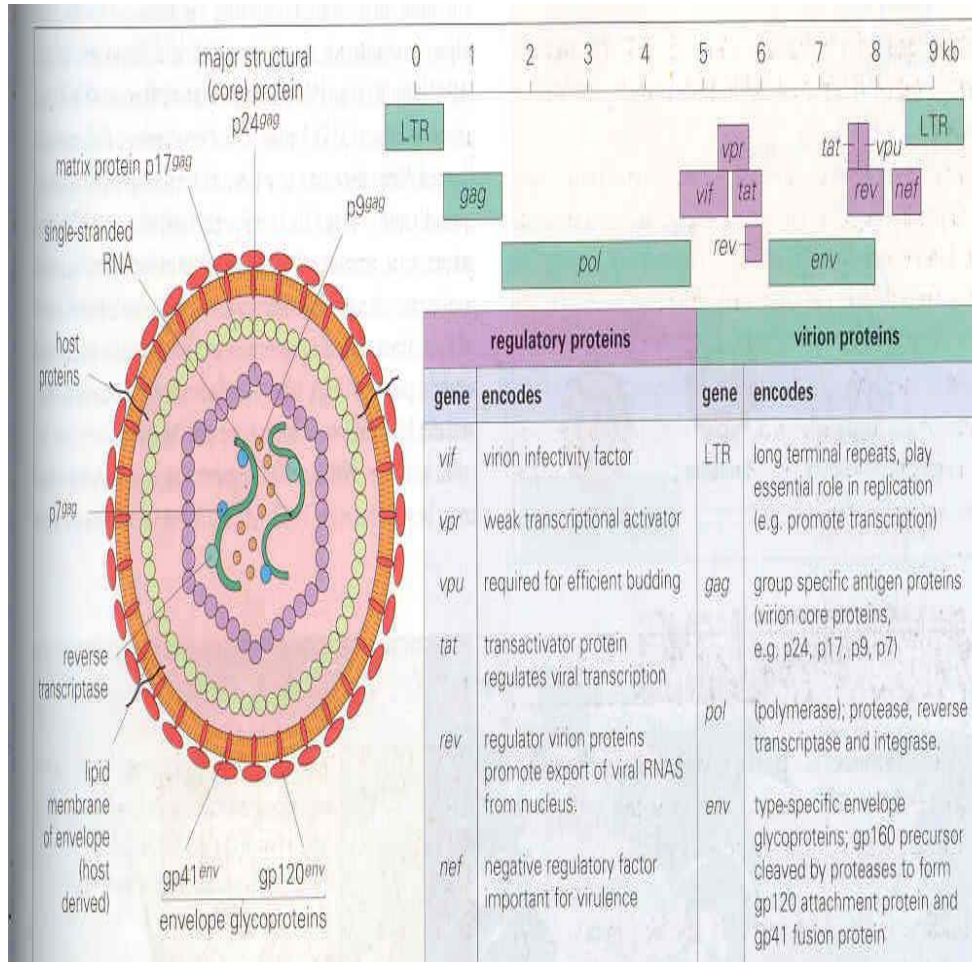


Fig. 3: HIV molecular structure with GENE'S table<sup>17</sup>

Life cycle of HIV<sup>18</sup>

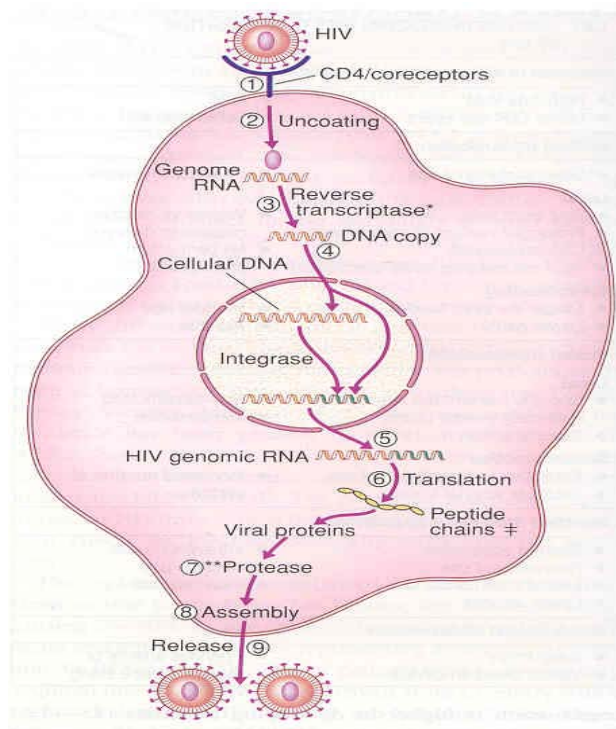


Fig. 4: Life cycle of HIV <sup>19</sup>

#### Virus binding to the host cell membrane

The plasma membrane of the host cell presents the first physical barrier to HIV infection. The viral binding and fusion machinery in HIV is contained in its outer envelope glycoproteins gp120 and gp41. The glycoproteins gp120 binds with high affinity to another specific glycoprotein on the T-cell surface called the CD4 receptor.

#### Virus fusion with host cell cytoplasm and its uncoating

The process is mediated by the second envelope viral glycoprotein gp41. However, engagement of gp41 to a second set of coreceptors such as CXCR4 (the coreceptor for HIV-1 strain that infect T-cell, T-tropic or X4 strain) and CCR5 (that infect macrophages, M-tropic, or R5 strain).

Binding of gp120 to the coreceptors triggers structural changes in the viral transmembrane part of gp41, and this interaction results in uncovering of the outer end of gp41. The exposed end of gp41 embeds itself in the host cell membrane through specific structures, leading to eventual fusion of the two membranes. After virus enters the cell, the virus loses its envelope in a process known as uncoating and then release its RNA genome in to the cytoplasm.

#### Viral DNA formation by the reverse transcriptase

After uncoating, a complementary strand of DNA is copied from viral RNA by HIV-DNA polymerase (reverse transcriptase). Subsequently, a second copy of DNA is made so that the genetic information is encoded in a double strand form of DNA.

The viral RNA is degraded by another ribonuclease enzyme, which cleaves RNA from the hybrid DNA leading to release of the viral DNA in the host cell cytoplasm. The newly formed viral DNA is called the provirus.

#### Viral DNA entry to the host cell nucleus

In the host cell the provirus, may stay in a free form or may enter the host cell nucleus, through pores in the nuclear membrane and undergoes integration with the host cell genome.

#### Integration of viral DNA into the host genome for viral mRNA production

Once the viral DNA is inside the nucleus, it integrates into the host chromosomes through the viral enzyme integrase. The linear viral DNA flanked by the two LTRs, found in the cytoplasm and nucleus of the infected cells, is the direct substrate for the viral integrase. The enzyme inserts the double stranded viral DNA at random into the host cell DNA. Upon integration of viral DNA into the the host genome, it starts to direct the transcription to produce its mRNA and other types of viral RNA.

#### Cutting of viral mRNA from the host cell genome

The transcription process of viral RNA occurs in the T-cell nucleus, as part of its own transcription.

The cutting of viral mRNA and other viral RNA molecules from the host DNA is also accomplished by the normal host cell RNA polymerase to produce an array of viral mRNA.

#### Migration of the viral mRNA to the cytoplasm

After viral mRNA is produced and sliced through use of the host cell genome, mRNA is released into the cytoplasm, where it directs the manufacture of various viral proteins, including core proteins, regulatory proteins, envelope proteins, and enzymes.

Virus exploits the biochemical machinery of the host cell to produce its functional components, the synthesis of such products is regulated by the virus genome.

#### Assembly of viral proteins to form the virion

The resulting viral or proteins are produced as a single large polypeptide precursor, which is then transported, with the help of viral RNA, to the host cell membrane in preparation for its assembly into daughter particles.

Each polypeptide precursor is enveloped with gp120 and gp41 glycoproteins after being encapsulated with the p17 and p24 viral core proteins. The particle are now ready to be expelled or budded out of the cell.

#### Viral budding out of the host cell

The assembled particles are released out of the host cell membrane by a process called *budding*, which leave a hole or several hole in the

T4 cell membrane which may contribute to the CD4 cell death. The host cells normally do not survive the invasion by HIV. This destruction of CD4 cells causes severe immunodeficiency because of the role of helper T-cells in mediating the system immunity.

#### **Virus maturation by HIV protease**

Shortly after budding the poly protein precursor, inside the daughter particles undergoes cleavage by a specific viral enzyme known as HIV protease. The resulting degradation products are the viral functional enzymes and proteins necessary for its survival. The virus particles at this stage are called virions. The virions have all the necessary constituents of a mature virus and are capable of invading other T4 cells and repeating the life cycle.

#### **Symptoms of AIDS <sup>20</sup>**

Symptoms early after infection are acute HIV-fever, headache, muscle and joint pain,

#### **Acute HIV - recognize the symptoms**

#### **Symptoms of the immune system**

The immune system is the body's natural defense against invading foreign agents such as viruses and bacteria. HIV attacks the immune system, weakening it and making the body more susceptible to infection. After infection, some symptoms affect the immune system, Swollen lymph nodes in the neck, axilla, or groin (lymphadenopathy)

#### **Symptoms of the GI tract**

Rapid weight loss, diarrhea, poor appetite, profound fatigue.

#### **Respiratory symptoms**

Some of the most serious symptoms of HIV involve the respiratory system. Symptoms associated with breathing and respiration usually occur later in course of the disease.

#### **Symptoms of the skin and mucous membranes**

Skin rash, Red, brown, pink or purple lesions on the skin - suggestive of Kaposi's sarcoma, White patches on the tongue, innerside of the mouth, or gums.

#### **Neurological symptoms**

Depression, Numbness, tingling, or burning in the feet, hands, or face, Confusion, weakness, or changes in level of consciousness

#### **Targets in design of anti-HIV agents <sup>21</sup>**

The understanding of function and molecular structure of the viral enzyme has contributed to the discovery of a large number of anti HIV drugs through rational drug design.

All clinically approved anti HIV drugs interfere with the viral life cycle by inhibiting one of the two enzymes the transcriptase or the protease enzyme. These two enzymes play a vital role in the process of viral replication inside the T-cell. Virtually, every step of the cycle has been targeted for drug design.

Anti HIV agents can be grouped into three groups based on phase of their interference with the virus replication cycle that is, pre-transcription inhibitors, transcription inhibitors, post transcription inhibitors.

#### **A. Pre-transcription inhibitors**

These are agents capable of blocking viral entry into the host cell. This class includes inhibitors of gp120 binding to CD4, inhibitor of gp120 binding to coreceptors and inhibitors of viral fusion and viral uncoating.

#### **B. Transcription inhibitors**

Transcription is the central stage through which viral DNA is transcribed from viral RNA under the control of reverse transcriptase enzyme. Inhibitors of this enzyme represent a very important class of anti HIV agents.

#### **C. Post transcription inhibitors**

These agents inhibit viral DNA integration into the host cell genome and interfere with virus maturation by blocking the crucial step of producing viral functional proteins from the polyprotein precursor. The most challenging problem associated with HIV therapy is the development of drug resistance.

#### **Approach for reduction of drug resistance by HIV <sup>22</sup>**

Highly Active Anti-Retroviral Therapy (HAART) → Combination of typically 3 or 4 anti HIV agents.

Mega - HAART or Salvage therapy → larger combinations of antiretroviral drugs. Increased side effects and cost are drawback of this therapy.

Drug holidays → intentional discontinuations of treatment to increase the sensitivity of HIV to antiretroviral drugs.

Intermittent therapy → reduce exposure to antiretroviral drugs to mitigate side effects. Schedules of *Week-on, week-off* (also known as "wowo") and *Five-days-on, two-days-off* (also known as "foto").

#### **Anti-HIV drugs: Existing scenario**

Antiretroviral drugs are broadly classified by the phase of the retrovirus life-cycle that the drug inhibits.

There are thus five broad classifications of antiretroviral drugs in development, though only the second and fourth classes currently have licensed.

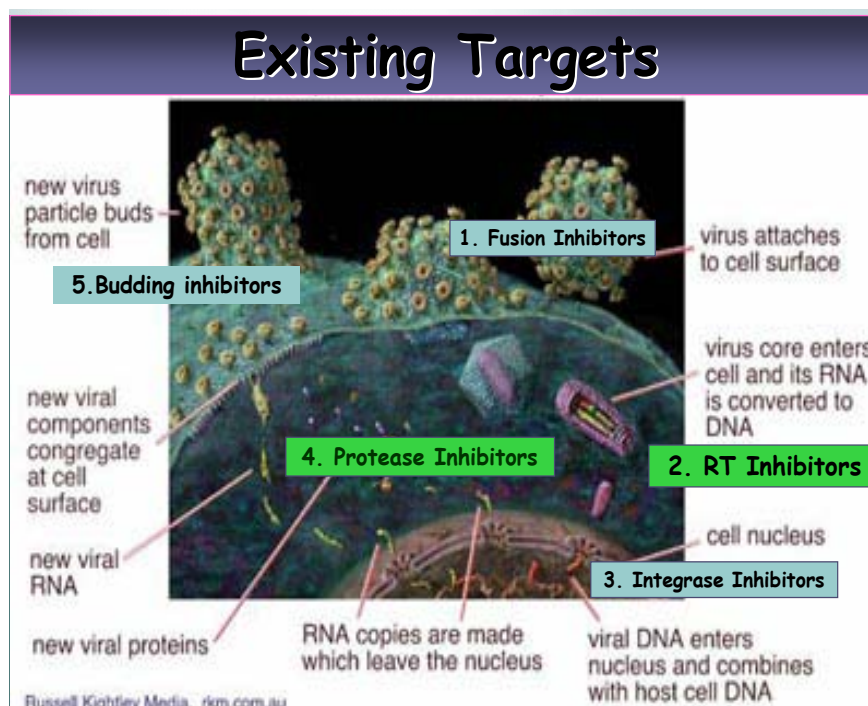


Fig. 5: HIV targets for drug design<sup>23</sup>

### Inhibitors of viral entry

#### HIV vaccines<sup>24</sup>

The most ideal approach to inhibit HIV binding to the T-cell is to develop a vaccine that can neutralize the virus in circulation.

The initial work on vaccine development focused on iso-typic variants of the HIV envelope glycoprotein gp120 obtained by recombinant DNA techniques. This target was chosen because of concern about the safety of live/attenuated vaccines.

The gp120 glycoprotein is a coat protein, and if great care is taken, a virus-free vaccine is obtainable. Moreover, glycoprotein gp120 is a primary target for neutralizing antibody associated with the first step in HIV infection. Intensive investigation of recombinant gp120 subunit vaccine has revealed a previously unexpected complexity in eliciting neutralizing antibodies that are active against primary isolate viruses.

gp120-derived vaccines induced little cell-mediated immunity and strong antibody response in T-cell lines, but failed to neutralize virus derived from peripheral blood mononuclear cells. Recombinant attenuated vaccinia virus expresses key viral envelope protein followed by a booster of soluble envelope protein derived from HIV. It produced a good humoral and CMI response and IgA antibodies in animal models.

#### AIDSVAX<sup>25</sup>

AIDSVAX from VaxGen Inc. is a preventive vaccine made up of synthetic gp120. Two Phase III clinical trials were initiated. Failed due to lack of adequate protection.

#### DNA Vaccine<sup>26</sup>

In recent years a new type of vaccine, created from an infectious agent's DNA called *DNA vaccination*. It works by insertion (and expression, triggering immune system recognition) into human or animal cells, of viral or bacterial DNA. As of 2006, DNA vaccination is still experimental, but shows some promising results.

However, the nature of the disease people infected with HIV develop only low titers of neutralizing antibody and that presents problem for vaccine development.

### Viral adsorption inhibitor<sup>27,28</sup>

The development of viral adsorption inhibitors and other anti-HIV agents together with molecular details of gp120 structure are summarized below:

#### Poly anionic compounds<sup>29</sup>

Among these anionic compounds are poly sulfates, poly sulfonates, and poly carboxylates. All are believed to exert their antiviral activity through inhibiting gp120 binding to the CD4 receptor.

#### Mechanism of action

These polyanionic substances inhibit gp120 binding by shielding the positively charged sites on the V3 loop of the viral envelope glycoprotein gp120. The V3 loop is one of the five poly peptide loops that constitute the backbone of the glycoprotein gp120 which is necessary for the initial viral attachment to the cell surface. Most promising of the poly anionic substance are poly naphthalene sulfonate (**1**), poly vinyl alcohol sulfate (PVAS) (**2**).

#### Soluble CD4 peptide fragments<sup>30</sup>

Soluble form of CD4 were isolated and evaluated for clinical efficacy to suppress HIV infection. Pro542 is a conjugation product of the CD4 soluble receptor with the constant regions of the human IgG2. Pro542 was found to be more effective than the soluble CD4 alone in blocking HIV transmission in the sci-hu-PBL mouse model.

#### Inhibitors of Gp120 binding to the T-cell coreceptors

##### Gp120 coreceptors<sup>31</sup>

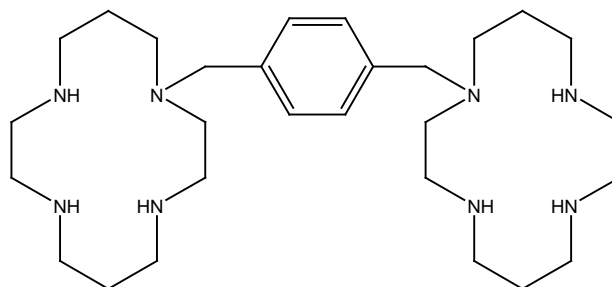
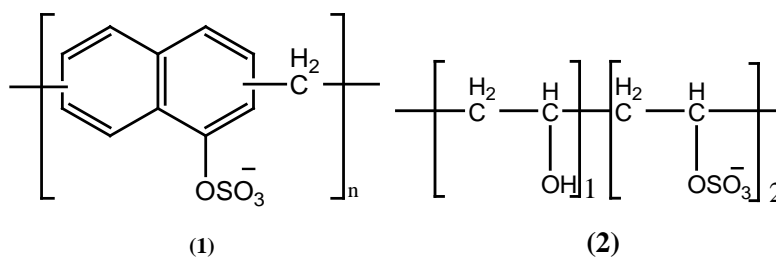
In the virus entry part of the life cycle, the coreceptors CXCR4 and CCR5 are newly discovered binding sites for gp120 on the T-cell membrane surface.

The importance of inhibiting gp120 binding to these coreceptors emerges from their role in the process of activating the second viral envelope protein gp41 binding to the T-cell surface, which ultimately leads to virus entry.

##### Gp120-CXCR4 binding inhibitors<sup>32</sup>

The most interesting member of this class is AMD-3100 (**3**). It shows an *in vitro* anti HIV activity before the discovery of the HIV-1

coreceptors.



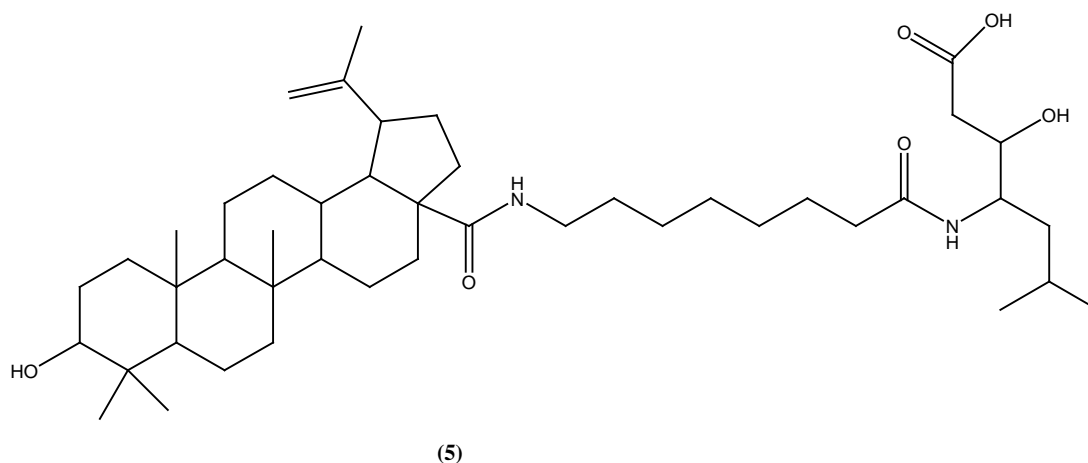
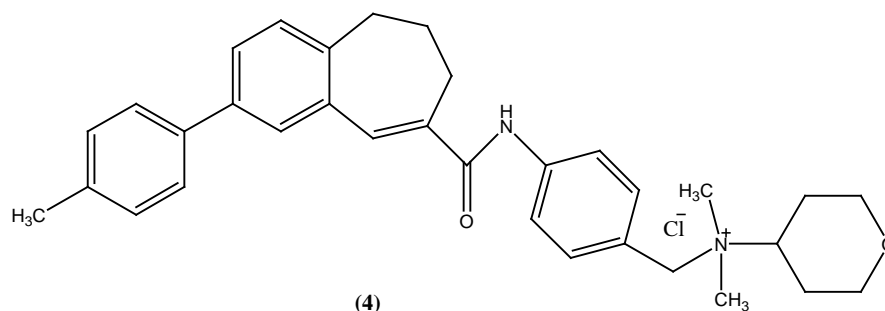
#### Gp120-CCR5 Binding Inhibitors<sup>33</sup>

The most attractive agent of this class undergoing clinical trials is the quaternary ammonium derivative TAK-779 (**4**), the first non peptide molecule described to block the replication of M-tropic R5-HIV strain at the CCR5 level.

#### Inhibitors of viral fusion<sup>34</sup>

This binding triggers a spring loaded action on the glycoprotein gp41, which is normally covered by the larger gp120.

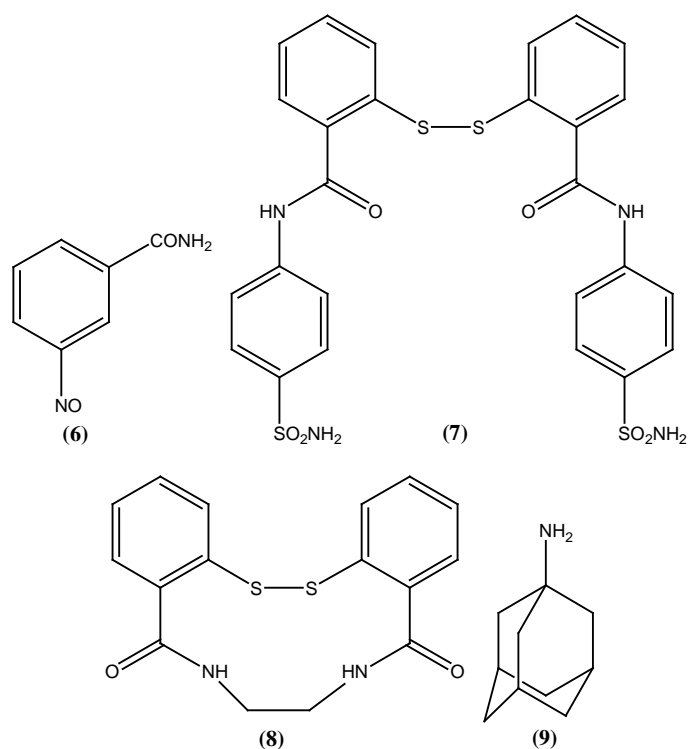
The gp41 anchors itself to the T-cell membrane through the hairpin structure HR1 and HR2; this initiates the fusion of the lipid bilayers of the virus and cell membrane. Before the knowledge of structural information of gp41 synthetic peptides overlapping the two HR regions HR1 (eg.DP-107 peptide) and HR2 (eg.DP-178 peptide) were found to block HIV replication in cell culture. The peptide act in dominant negative fashion to prevent formulation of the trimer of hairpins arrangement. The betulinic acid derivative RPR103611 (**5**) represents a nonpeptide inhibitor for gp41 fusion.



### Inhibitor of viral uncoating

Uncoating is controlled by the p7 nucleocapsid protein (NCp7), which is peptide segment of the p17 protein. NCp7 is a zinc

containing protein, and zinc displacing compounds were found to inhibit the virus uncoating process. Among these agents are: NOBA (3-nitrosobenzamide)<sup>35</sup> (**6**), the dithiobenzamide-sulfonamide derivative (DIBA)<sup>36</sup> (**7**), SRR-SB3<sup>37</sup> (**8**) and amantidine<sup>38</sup> (**9**).



### HIV reverse transcriptase inhibitors

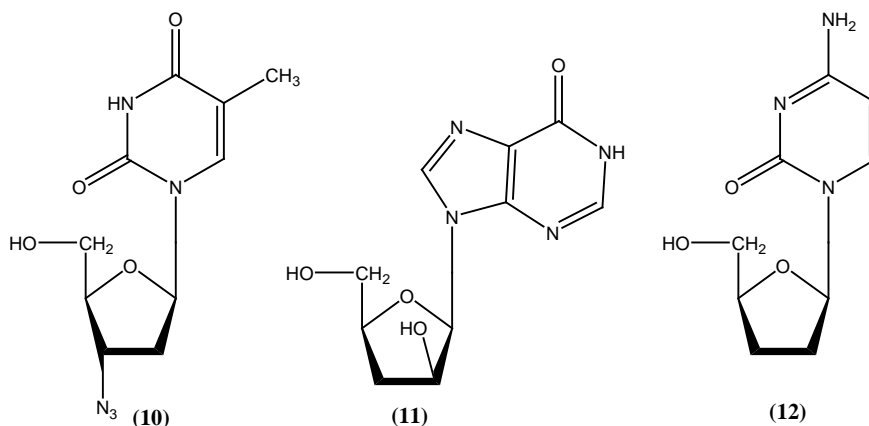
Inhibitors of HIV transcriptase act by impeding the nucleotide binding to the active site. The inhibition is achieved by two distinct mechanisms, either competitively or noncompetitively. The competitive inhibitors are nucleoside analogs or have nucleoside like structure. The nucleoside inhibitors are further classified into purine and pyrimidine nucleoside inhibitors based on the nucleic acid base existing in the molecule. On the other hand, the noncompetitive inhibitors are not structurally related to the nucleotide and are referred to as allosteric inhibitors.

#### Nucleoside reverse transcriptase inhibitors (NRTIs)

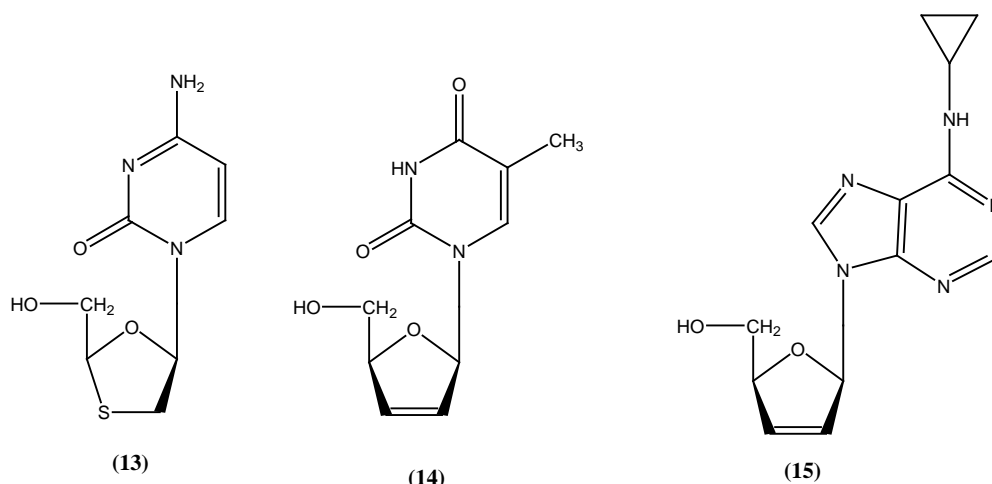
Members of this class act as irreversible, competitive inhibitors for the HIV reverse transcriptase. They compete with normal substrate at the enzyme catalytic site. These normal substrate are different types of deoxyribonucleosides triphosphate

(dNTP). Therefore, members of this class being nucleoside in nature require intracellular activation to the nucleoside triphosphate form. This activation process requires three phosphorylation steps whereby the compounds are converted successively to mono-, di- and triphosphate by cellular kinases. The NRTI is attributed into the viral DNA through an irreversible covalent bond. The irreversible bond occurs through the activated 5-OH of the sugar. On the other hand, structure of all NRTIs indicates their lack of the 3-OH group of the sugar. The absence of the 3-OH group results in a DNA intermediate product that does not elongate further through position 3. This process of blocking DNA elongation is commonly referred to as chain termination.

These NRTI drugs includes zidovudine<sup>39</sup> (**10**), didanosine<sup>40</sup> (**11**), zalcitabine<sup>41</sup> (**12**), lamivudine<sup>42</sup> (**13**), stavudine<sup>43</sup> (**14**) and abacavir (**15**) which are currently in the market.



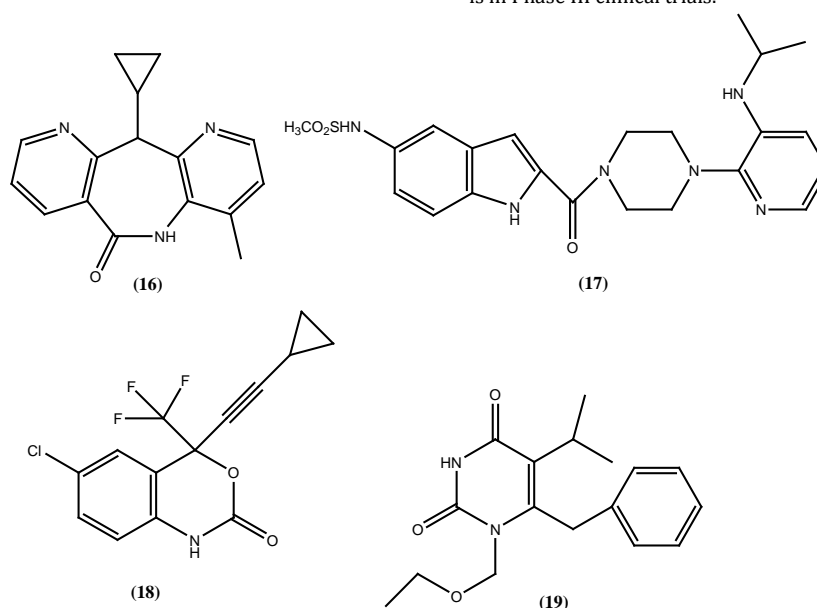




### Non-nucleoside reverse transcriptase inhibitors (NNRTIs)<sup>44,45</sup>

The NNRTIs target the allosteric nonsubstrate binding sites. The NNRTIs binding site may be functionally and possibly also spatially related to the substrate binding site. Members of this class are described as non competitive, reversible inhibitors. This class is

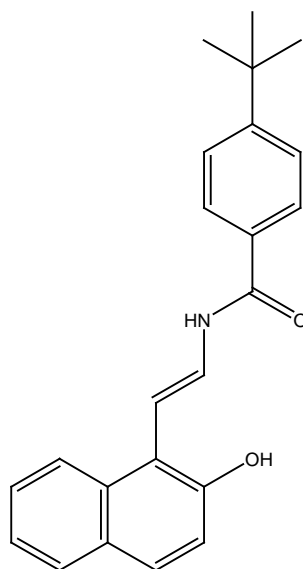
highly specific to HIV-1 RT without affecting the host DNA polymerase which explain the low toxicity and side effect of these drugs. Only three drugs belonging to the NNRTIs class have been approved to the clinical use, nevirapine<sup>46</sup> (16), delavirdin<sup>47</sup> (17), and efavirenz<sup>48</sup> (18). The second generation NNRTI emivirine (19)<sup>18</sup> is in Phase III clinical trials.



### Inhibitors of HIV ribonuclease<sup>49</sup>

The tristranded product requires cleavage of the original RNA strand from the double helix DNA molecule. Ribonuclease is the enzyme responsible for the step of removal of viral RNA from

DNA. The activity of viral ribonuclease is believed to be mediated by a special domain on the RT enzyme. This class of inhibitors is the comp. N-(4-t-butylbenzoyl)-2-hydroxy-1-naphthaldehyde hydrazone (BBNH)<sup>49</sup> (20), which was reported to be a very potent inhibitor for ribonuclease.



(20)

**HIV integrase inhibitors<sup>50</sup>**

It catalyzes the insertion of the HIV-1 DNA into the host cell genome. Integration is required for stable maintenance of the viral genome and viral gene expression. Accordingly HIV integrase has been considered as an attractive target in the design of anti HIV drugs. Promising example of these inhibitors are L-chicoric acid<sup>50</sup> (**21**) and diketo acid derivatives L-731,988<sup>50</sup> (**22**), L-708906 (**23**). All have been described as potent integrase inhibitors.

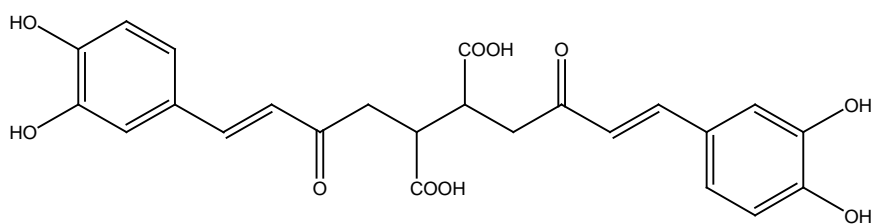
**Inhibitors of HIV gene expression (Transactivation inhibitors)**

A number of compounds have been reported to inhibit this process of the gene transactivation through inhibiting tat binding to the promoter LTR ends. Fluroquinoline K-12<sup>51</sup> (**24**) and temacrazine<sup>52</sup> (**25**) are the representative examples.

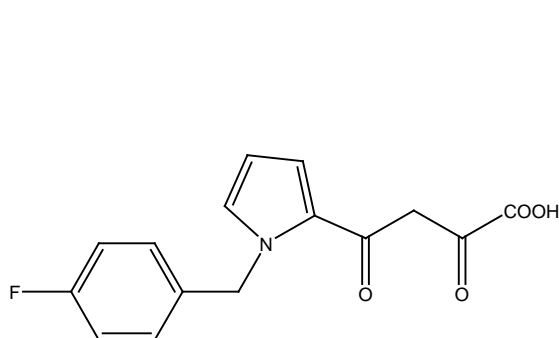
**Inhibition of viral maturation (HIV-1 protease inhibitors)**

HIV protease represents the second enzyme in the virus life cycle, after the RT that has been extensively targeted for drug design. HIV protease is a proteolytic enzyme responsible for cleaving the large polyprotein precursor into biologically active protein product. HIV polyprotein is encoded by the *gag* and *gag-pol* genes. These genes encode the precursor with HIV structural core protein and various viral enzyme. HIV protease cleaves this polyprotein precursor during or shortly after viral budding to produce the mature virion. Therefore inhibition of this post translational step leads to total arrest of viral maturation, thereby blocking infectivity of the virions.

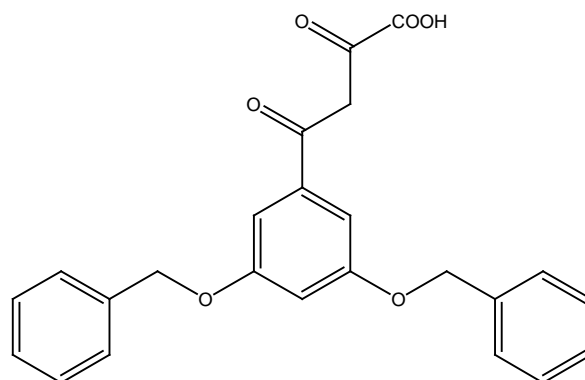
Currently used protease inhibitors for the treatment of HIV infection are indinavir<sup>53</sup> (**26**), ritonavir<sup>54</sup> (**27**), saquinavir<sup>55</sup> (**28**), nefinavir<sup>56</sup> (**29**) and amprenavir<sup>57</sup> (**30**).



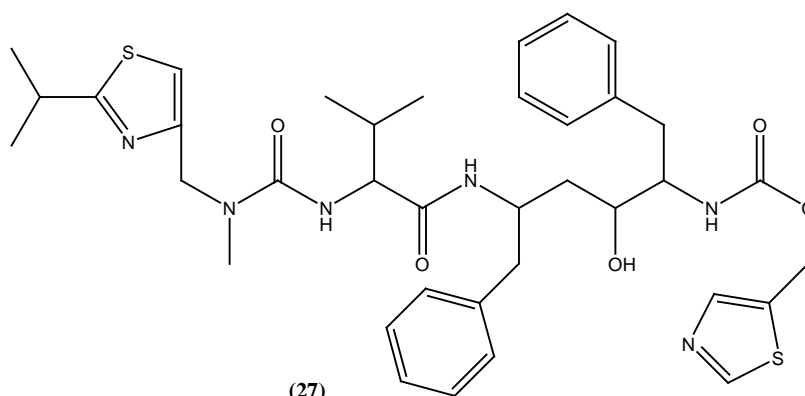
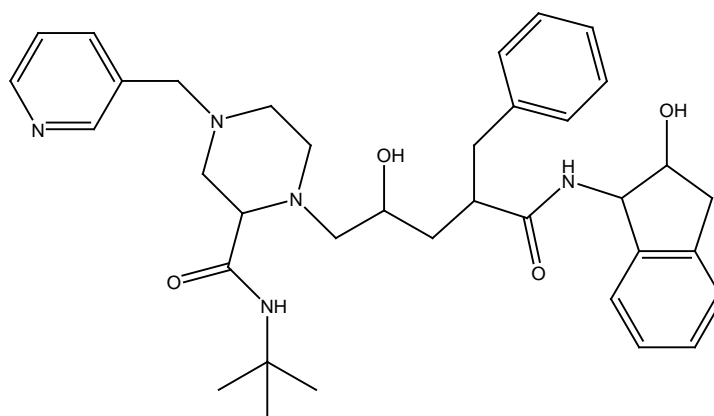
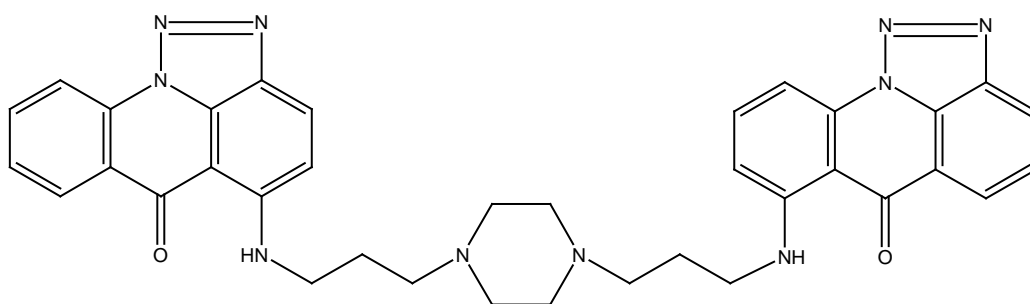
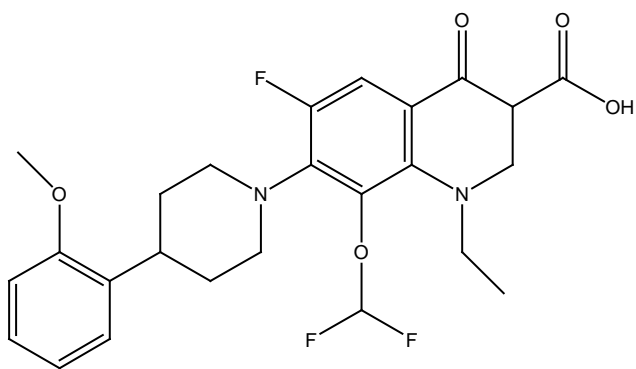
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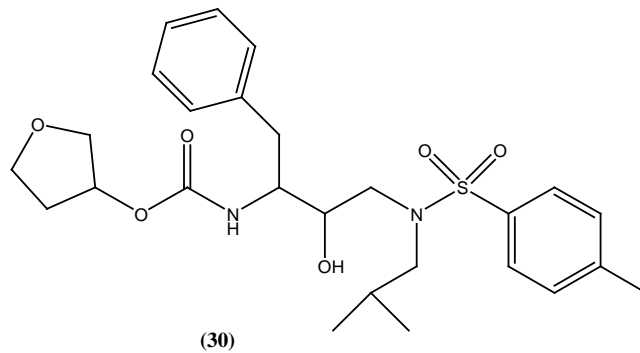
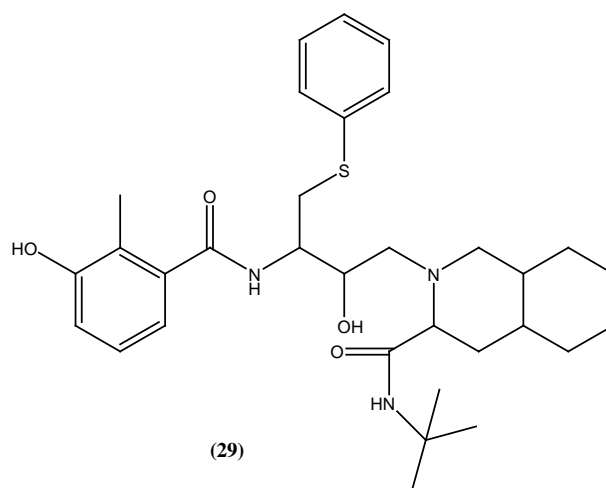
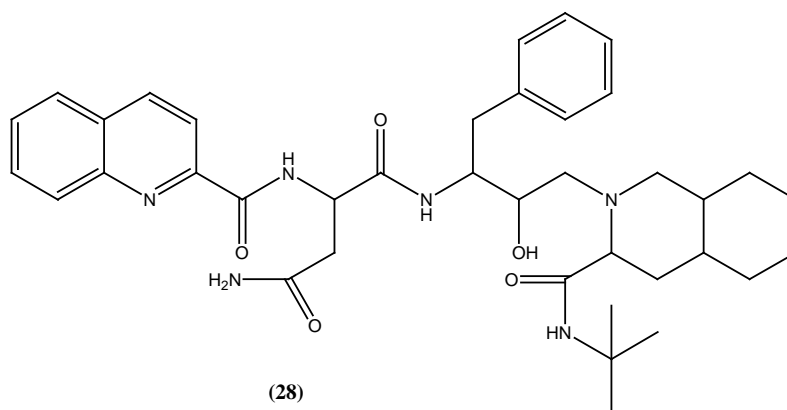


(22)

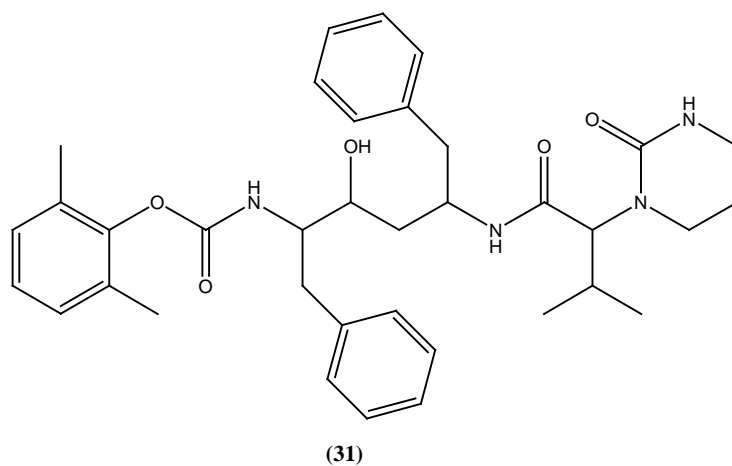


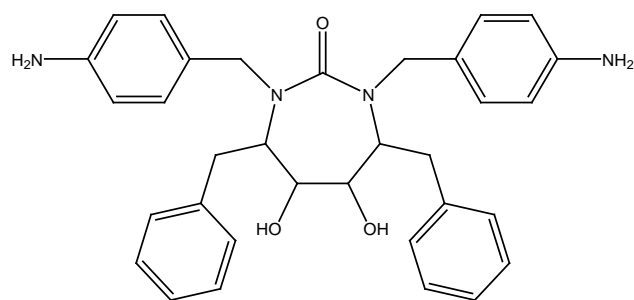
(23)



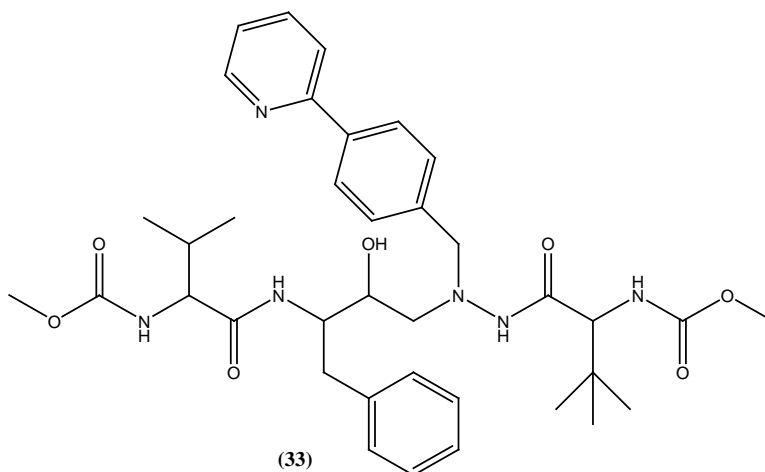


Some novel protease inhibitors with nonpeptide structure have been developed such as lopinavir<sup>58</sup> (31), mozinavir<sup>59</sup> (32), atzanavir<sup>60</sup> (33), tipranavir<sup>61</sup> (34) and C2-symmetric protease inhibitor L-mannaric acid<sup>62</sup> (35).

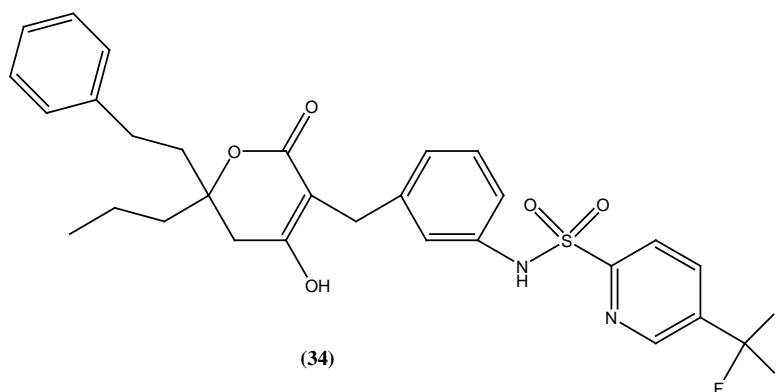




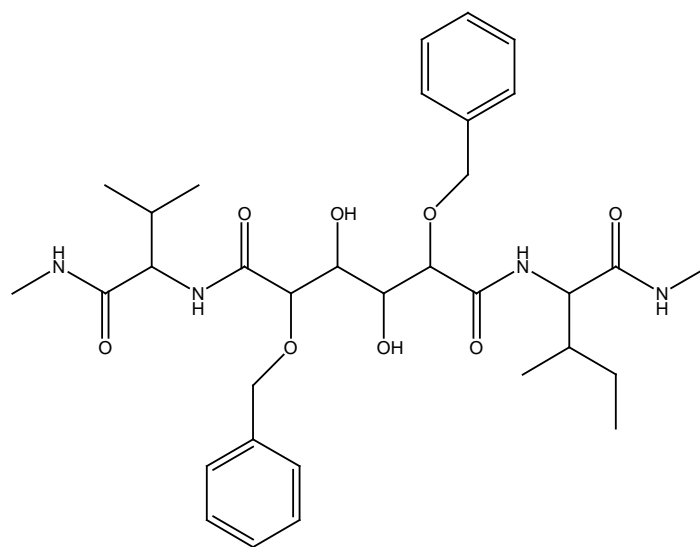
(32)



(33)



(34)



(35)

Table 1: Approved drugs for the treatment of AIDS<sup>18</sup>

Generic Name	Brand Name	Company	Class
Zidovudine	Retrovir	Glaxo Wellcome	NRTI
Didanosine	Videx	Bristol-Myers Squibb	NRTI
Zalcitabine	Hivid	Hoffman-La Roche	NRTI
Stavudine	Zerit	Bristol-Myers Squibb	NRTI
Lamivudine	Epivir	Glaxo Wellcome	NRTI
Abacavir	Ziagen	Glaxo Wellcome	NRTI
Neveirapine	Viramune	Boehringer Ingelheim	NNRTI
Delavirdine	Rescriptor	Pharmacia	NNRTI
Efavirenz	Sustiva	Hoffman-La Roche	NNRTI
Idinavir	Crixivan	Mercke	PI
Ritonavir	Norvir	Abbott	PI
Saquinavir	Invirase	Hoffman-La Roche	PI
Nelfinavir	Viracept	Agouron Pharma	PI
Amprnavir	Agenerase	Glaxo Wellcome	PI

## CONCLUSION

AIDS is retroviral disease caused by HIV. Currently, available drugs target on the replication cycle of HIV but no one drug cure the AIDS. As the HIV mutates very rapidly, and resistance towards, all the currently available drugs occur. So, now a day, researchers are going towards new targets for developing of new molecules, in which chances of mutation is less. These recent advances are quite promising and may eradicate the HIV infection within a reasonable period of time.

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