Anti-HIV Agents (Antiretroviral Therapy for HIV Infection) — List of Drugs and Mechanism of Action

The Human immunodeficiency virus (HIV) infection occurs in and kills millions of people every year worldwide. The virus enters CD+ cells of the host immune system and replicates, thereby destroying the cells and weakening the immune system. This leaves the host vulnerable to many infections. It is crucial to understand the mechanism of the HIV infection in order to develop effective antiretroviral therapies. Unfortunately, resistance against HIV drugs is common and cross-resistance among the same class of drugs is also common. Measures such as pre- and post-exposure prophylaxis help to combat the spread of infection.

Overview of HIV Infection

Acquired immunodeficiency syndrome (AIDS) is caused by the retrovirus human immunodeficiency virus (HIV). There are two related, but genetically different forms of HIV —HIV-1 and HIV-2. The structure of the virion is as shown in the image below.
Briefly, the core contains capsid protein p24; nucleocapsid protein p7/p9; two copies of RNA; and three enzymes – protease, reverse transcriptase and integrase. The RNA genome contains three genes – gag, pol, and env. On the envelope are two glycoproteins, gp120 and gp41, which play a crucial role in infection.

The infection begins when gp120 attaches to CD4 (found on the surface of helper T cells and other CD4+ cells such as dendritic cells and monocytes/macrophages). Many HIV strains require a transmembrane chemokine receptor CCR5 for successful attachment (some may use CXCR4 and yet others may use both).

Binding causes gp41 to undergo a conformational change, leading to exposure of the fusion peptide at the tip. The virus is then internalized and the RNA gets transformed to double-stranded DNA, which is incorporated into the host genome. Protease is responsible for cleaving the viral glycoprotein during the maturation of the virus into essential enzymes, including reverse transcriptase and integrase, as well as structural proteins.

Antiretroviral therapy (ART), at present, is targeted at various stages of the mechanisms (see figure below): inhibition of the entry of the virus into the host cells, of transformation of viral RNA into DNA, of viral DNA integration with the host genome, and of synthesis of the mature virus (which then buds out of the cell and causes further infection).

Classification of Anti-HIV Agents

Reverse transcriptase inhibitors

- Nucleoside reverse transcriptase inhibitors (NRTIs): abacavir (ABC), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), tenofovir
disoproxilfumarate (TDF), stavudine (d4T), zidovudine (ZDV)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTIs): efavirenz, nevirapine, etravirine, rilpivirine
  - Protease inhibitors: atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir
  - Integrase strand transfer inhibitors: dolutegravir, elvitegravir, raltegravir
  - Entry Inhibitors: Fusion inhibitors: enfuvirtide
  - CCR5 antagonists: maraviroc

Pharmacology of Anti-HIV Drugs

The subsections of reverse transcriptase inhibitors and protease inhibitors focus on the general overview of the class and one or two representative drugs. A summary of other important drugs in the class is presented in a tabulated form at the end of each subsection.

Reverse transcriptase inhibitors

- These drugs inhibit the reverse transcriptase enzyme (i.e., RNA-dependent DNA polymerase)
- The two types of reverse transcriptase inhibitors – NRTIs and NNRTIs – act by different mechanisms.

Nucleoside reverse transcriptase inhibitors (NRTIs)—Zidovudine (ZDV)

- Prodrugs; they are converted to triphosphates in the host cell.
- Zidovudine has a good oral bioavailability.
- Most NRTIs are renally excreted; Zidovudine undergoes hepatic metabolism as well.
- Zidovudine crosses the placenta and is secreted in breast milk.

Mechanism of Action

The triphosphate metabolites act by two mechanisms: (i) they compete with natural nucleotides for binding to the dNTP-binding site (Deoxyribonucleoside Triphosphate-binding site) of the reverse transcriptase enzyme and (ii) by getting inserted into the DNA chain; they act as chain terminators as nucleotides cannot get attached to them due to the lack of a 3'hydroxyl group.

There is a considerable difference between human RNA and DNA polymerases and the viral enzymes, so the toxicity to humans is limited; however, mitochondrial DNA polymerase γ can be susceptible.

Adverse Effect/Toxicity

- Lactic acidosis, hepatomegaly with steatosis (liver function should be monitored)
- Anemia and neutropenia (due to bone marrow suppression)
- Gastrointestinal (GI) symptoms—nausea, vomiting, diarrhea; acute cholestatic hepatitis; agitation; headaches; myalgia; insomnia;
thrombocytopenia
- Resistance: rapid, especially when given as single agents; this is due to pol gene mutations. Partial cross-resistance can also occur.

Drug Interactions
- Ketoconazole, and otherazole antifungals, as well as protease inhibitors, increase plasma levels of zidovudine
- Rifampin increases zidovudine clearance

Contraindications
- With caution in obese patients and patients with liver dysfunction
- Dose adjustment is required in patients with uremia or cirrhosis.

Summarized Important Points for other commonly used NRTIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacokinetics</th>
<th>Adverse Effects</th>
<th>Interactions/Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didanosine</td>
<td>Food and chelating agents reduce its bioavailability</td>
<td>Pancreatitis, peripheral neuropathy, diarrhea, etc.</td>
<td>• Caution with alcoholic patients, patients with hypertriglyceridemia • Concurrent use of stavudine or tenofovir is contraindicated</td>
</tr>
</tbody>
</table>
| Emtricitabine | • It is also active against the hepatitis B virus.  
|            | • Intracellular half-life of 39 hours.                                              | Palmoplantar hyperpigmentation, headache, diarrhea, rash, etc.                                     | No significant interactions with other drugs.                                                  |
| Lamivudine | It is also active against the hepatitis B virus.                                    | Well tolerated because it does not affect the mitochondrial DNA synthesis or bone marrow precursor cells |                                                                                                |
| Stavudine  | Thymidine analog; penetrates the blood-brain barrier                               | Peripheral neuropathy, headache, diarrhea, lipoatrophy, etc.                                        | Concurrent use of didanosine or zalcitabine is contraindicated                                   |
| Tenofovir  | • It is a nucleotide analog and is converted to diphosphate.  
|            | • Long half-life; intracellular half-life of 60 hours.                              | Gi symptoms                                                                                         | • Concurrent use of didanosine is contraindicated • Decreases serum levels of atazanavir • Decreases renal excretion of acyclovir and ganciclovir |

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)—Efavirenz, Nevirapine

Better than NRTIs on HIV-1, but they do not have an effect on HIV-2.
Mechanism of Action

They directly inhibit the reverse transcriptase enzyme without undergoing intracellular phosphorylation.

Adverse Effect/Toxicity

- Rash, GI symptoms, headache, fever
- Hepatotoxicity (increase in liver enzymes)
- Resistance: Point mutation; Cross-resistance: possible among NNRTIs but not with other anti-HIV agents.

Drug Interactions

Inducers of CYP 3A4, 206 thus they enhance their own metabolism, as well as those of other drugs metabolized by this system and, therefore, concomitant administration of other potent CYP inducers (e.g., rifampin) or inhibitors (e.g., ketoconazole and other azole antifungals), should be avoided.

Summarized Important Points for other commonly used NNRTIs

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Other Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etravirine</td>
<td>Rash</td>
<td>Useful in case of resistance against first-generation NNRTIs</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>A rash is common. Increased ALT/AST</td>
<td>Not recommended in the current guidelines due to relatively inferior efficacy and three times daily dosing.</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Depression, headache, insomnia, rash</td>
<td>Absorption is pH-dependent, so should not be administered with proton pump inhibitors and not close to the administration of H2 inhibitors and antacids</td>
</tr>
</tbody>
</table>

Protease inhibitors—Indinavir

- More effective than NRTIs.
- Effective in both newly and chronically infected cells.
- Efficacy is increased when combined with one NRTI (double therapy); it is increased further when combined with two NRTIs or one NRTI and one NNRTI (triple therapy)
- Considerable plasma protein binding

Mechanism of Action

They reversibly inhibit the HIV aspartyl protease enzyme by attaching to it, thereby preventing its cleaving ability; thus, the progeny of HIV produced is non-infectious and immature and a further round of infection is avoided.

Adverse Effect/Toxicity

- GI symptoms are common
Most PIs are reported to be associated with dyslipidemias, fat deposition, or metabolic syndrome; this is because of the inhibition of lipid-regulation proteins.

- **Nephrolithiasis**: increased fluid intake is advised to prevent this
- Resistance: Develops due to selective point mutations in the pol gene.

**Drug Interactions**

- Extensively metabolized by **CYP 3A4 and other CYP enzymes**; therefore, concomitant administration of other potent CYP inducers (e.g., rifampin) or inhibitors (e.g., ketoconazole and other azole antifungals) should be avoided.
- Usually, they are inhibitors of CYP3A4 and they induce certain other CYP isoenzymes.
- The above two make specific drug interactions complicated and unpredictable.
- Severe drug interactions include simvastatin or lovastatin (rhabdomyolysis), midazolam or triazolam (excessive sedation), fentanyl (respiratory depression), etc.

**Summarized Important Points for other Commonly Used Protease Inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
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</table>
| Atazanavir | GI symptoms, rash, **hyperbilirubinemia**, prolongs PR interval | • Food increases absorption and bioavailability  
• Lower risk of hyperlipidemia than other protease inhibitors |
| Darunavir | GI symptoms, rash, oral and **perioral paresthesia** | • Always given with low-dose ritonavir  
• Can be used in patients resistant to other protease inhibitors |
| Nelfinavir | GI symptoms, rash | • Potent CYP3A4 inhibitor  
• Induces its own metabolism |
| Ritonavir | GI symptoms, **paresthesias**, fatigue, lipid abnormalities, increased hepatic enzymes | Induce its own metabolism |
| Saquinavir | • Frequent side effects  
• Photosensitivity | Should be taken with high-fat meals |
| Tipranavir | GI symptoms and **hepatotoxicity** | Many drug interactions (CYP 3A4 inducer, induces P-glycoprotein transporters) |

**Integrase strand transfer inhibitors (e.g., Raltegravir)**

- Pyrimidine derivative

**Mechanism of Action**

It binds to the **integrase enzyme**, which is required for the **replication** of both **HIV-1** and **HIV-2**.

**Adverse Effect/Toxicity**

- Usually well tolerated
- GI symptoms, dizziness, fatigue
- Potential myopathy or rhabdomyolysis (increased creatine kinase)
- Possible depression (suicidal ideation)
- Cross-resistance: common among integrase inhibitors

Drug Interactions

- It is not metabolized by the cytochrome P450 isoenzymes, so remains unaffected by drugs that inhibit or induce them.
- Rifampin increases its metabolism (by inducing UDP-glucuronosyltransferase), so dose increase is required.

Summarized Important Points for other Commonly Used Protease Inhibitors

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</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>Mild reversible creatinine elevation (because of inhibition of renal transport protein OCT2)</td>
<td>Can still be used in some patients who are resistant to other integrase inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolism is by UGT1A1 and CYP3A4 systems, so dose adjustment is required in their inducers/inhibitors</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>GI symptoms</td>
<td>• Half-life is boosted from 3 hours to 9 hours when co-administered with cobicistat—a pharmacokinetic enhancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Currently available only in a fixed-dose combination with tenofovir, emtricitabine, and cobicistat</td>
</tr>
</tbody>
</table>

Fusion Inhibitors (e.g., Enfuvirtide)

- HIV-derived synthetic peptide
- Not effective against HIV-2
- Administered subcutaneously

Mechanism of Action

Binds to a gp41 subunit of the HIV-1 envelope glycoprotein; this prevents fusion of the virus with the cellular membrane. However, the entry of the virus into the cell is still possible.

Adverse Effect/Toxicity

- Injection site complications (such as pain, erythema, induration, and nodules) are very common
- Resistance: mutations in the env gene; Cross-resistance: None with other anti-HIV drugs.

Drug Interactions

- Not metabolized by cytochrome P450, so remains unaffected by drugs that inhibit or induce them.
CCR5 Antagonist

- Before administration, a test must be undertaken to check if the virus strain uses CXCR4 instead.

Mechanism of Action

- Targets the chemokine receptor CCR5 - a human protein and not viral - and inhibits attachment of the virus to the cell.

Adverse Effect/Toxicity

- Generally well tolerated
- Coughing, diarrhea, muscle and joint pain; hepatotoxicity

Drug Interactions

Metabolized by CYP 3A4, so dose adjustment is required with concomitant administration of potent CYP inducers (e.g., rifampin) or inhibitors (e.g., ketoconazole and other azole antifungals).

HIV Prophylaxis

1. Post-Exposure Prophylaxis (PEP)

PEP is intended to suppress viral replication in the very beginning of viral replication, such that the infection is aborted. It can be taken by anybody who has had (accidental) exposure to HIV, e.g., healthcare workers or blood transfusion. PEP should be started as soon as possible after the exposure, usually within 48—72 hours, but ideally within 2 hours.

The preferred regimen for otherwise healthy adults and adolescents

§ tenofovir (300 mg) with emtricitabine (200 mg) once daily plus raltegravir 400 mg twice daily or dolutegravir 50 mg daily.

[Alternative regimen]
§ tenofovir (300 mg) with emtricitabine (200 mg) once daily plus darunavir (800 mg) and ritonavir (100 mg) once daily.

2. Pre-Exposure Prophylaxis

FDA approved a drug for pre-exposure prophylaxis of HIV, intending to reduce the risk in uninfected individuals who are at high risk of HIV infection or who engage in sexual activity with HIV-infected partners. The drug is a combination of emtricitabine and tenofovir disoproxil fumarate.

3. Perinatal Prophylaxis

- HIV transmission is possible from the mother to the child (a) through the placenta, (b) during delivery and (c) by breastfeeding, with the highest risk being during delivery.
- HIV-positive women not on ART should receive zidovudine (300 mg BD) started during the 2nd trimester and continued into the postnatal period, with the treatment of the neonate for 6 weeks.
Combination therapy is even more effective.

If for some reason, ART is not started earlier, zidovudine administered during labor and then to the infant can also be protective.

HIV-positive mothers should not breastfeed.

Review Questions

The correct answers can be found below the references.

1. A 27-year-old man presents with abnormal fat distribution on his body: the fat is concentrated around the center and at the base of the neck (buffalo hump). Which of the following medications is responsible for this presentation?
   
   A. Triazolam  
   B. Amiodarone  
   C. Enfuvirtide  
   D. Montelukast  
   E. Ritonavir

2. Which of the following drugs do not form a part of post-exposure prophylaxis of HIV infection?
   
   A. Maraviroc  
   B. Emtricitabine  
   C. Ritonavir  
   D. Raltegravir  
   E. Dolutegravir

3. A 33-year-old woman is diagnosed with HIV. On further analysis, she is found to be infected with the HIV-2 strain that utilizes CXCR4 to enter into CD4+ cells. Which of the following drugs can be administered to this patient?
   
   A. Enfuvirtide  
   B. Raltegravir  
   C. Efavirenz  
   D. Maraviroc  
   E. Rilpivirine

References

Centers for Disease Control and Prevention. [Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States, 2016](https://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf). Available at:


Medscape. [Delavirdine (Discontinued)](https://www.medscape.com/drug/delavirdine-discontinued). Available at:


**Correct Answers:** 1.E; 2.A; 3B

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