HIV life cycle: Targets for antivirals

Agents approved by FDA

**NRTI:** Nucleoside Reverse Transcriptase Inhibitor

**NNRTI:** Non-nucleoside Reverse Transcriptase Inhibitor

Likely to be available in the near future
### FDA-approved antiretroviral drugs available in the United States

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic name</th>
<th>Trade name</th>
<th>Date of FDA approval letter</th>
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<tbody>
<tr>
<td>Fusion inhibitors</td>
<td>Enfuvirtide (T-20)</td>
<td>Fuzeon</td>
<td>13 March 2003</td>
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<td>NNRTIs</td>
<td>Delavirdine mesylate</td>
<td>Rescriptor</td>
<td>4 April 1997</td>
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<td></td>
<td>Efavirenz</td>
<td>Sustiva</td>
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<td>Nevirapine</td>
<td>Viramune</td>
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<td>NRTIs</td>
<td>Abacavir sulfate</td>
<td>Zidovudine</td>
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<td>Abacavir sulfate + lamivudine</td>
<td>Trizivir</td>
<td>14 November 2000</td>
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<td>Didanosine (ddl)</td>
<td>Didanosine (ddl)</td>
<td>Videx</td>
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<td>Lamivudine (3TC)</td>
<td>Lamivudine + zidovudine</td>
<td>Combivir</td>
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<td>Stavudine (d4T)</td>
<td>Stavudine (d4T)</td>
<td>Zerit</td>
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<td>Tenofovir disopropil fumarate</td>
<td>Tenofovir disopropil fumarate</td>
<td>Viread</td>
<td>26 October 2001</td>
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<td>Zalcitabine (ddC)</td>
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<td>19 June 1992</td>
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<td>Zidovudine (AZT, ZDV)</td>
<td>Zidovudine (AZT, ZDV)</td>
<td>Retrovir</td>
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<td>Protease inhibitors</td>
<td>Amprenavir</td>
<td>Agenerase</td>
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<td>Indinavir sulfate</td>
<td>Crixivan</td>
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<td>Lopinavir + ritonavir</td>
<td>Kaletra</td>
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<td>Nelfinavir</td>
<td>Viracept</td>
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<td>Ritonavir</td>
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<td>Saquinavir</td>
<td>Fortovase</td>
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<td>Saquinavir mesylate</td>
<td>Invirase</td>
<td>6 December 1995</td>
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NRTIs and NNRTIs: Mechanisms of action
Nonnucleoside RT Inhibitors

Tibo, α-APA, and nevirapin fit within the RT region adjacent to dNTP-binding site
Protease inhibitors: Mechanism of action

- Immature viral particle
- Protease inhibitor
- Multiprotein molecule
- Inhibited protease prevents cleavage of the polypeptide and subsequent maturation of the virion
- Protease bound to inhibitor
- Viral RNA
- Protease enzyme
HIV Protease Inhibitors

Indinavir (Crixivan; Merck)

Ritonavir (Norvir; Abbott)

Saquinavir (Invirase; Roche)

nefnavir (Viread; Agouron Pharm.)

Inhibitor blocks active center of protease dimer
Fusion inhibitors: Mechanism of action

T20 (Enfuvirtide) is a 36-residue peptide that binds to transmembrane domain of gp41 and prevents its refolding that is required for fusion.
Highly active antiretroviral therapy: HAART

HAART is based on combined use of two NRTIs and a protease inhibitor

Benefits include dramatic reduction in virus load (a) in ~70% of patients (b) and increase in T-cell count (c)
HAART and viral reservoirs
HAART problems

Distribution of drug resistance mutations within RT and protease

Drug resistance evolves rapidly due to incomplete block of replication

Adherence

Toxicity and side effects

Pharmacology (variable drug absorption and interactions)
Among 30+ M people infected worldwide, HAART is available only to the economically privileged.

Decline in AIDS in the US

Rapid growth of AIDS in Russia

Spread of HIV in Africa (prevalence rate in 15-49 year olds)
For the last two decades, NIH alone invested ~$500 M/year for HIV vaccine effort. However, such vaccine still remains a distant dream.

There have been few, if any, instances of infected individuals naturally developing protective immunity to the virus.

Problems:
1. Env is trimerized and heavily glycosylated blocking antibody access to potential epitopes
2. The neutralizing ABs preferentially target the V-loops and are therefore of narrow specificity

Some neutralizing ABs show gp120 vulnerabilities, but the design of corresponding immunogens is very challenging, while some of these ABs also target self-antigens.

A model of the HIV-1 envelope spike showing the location of epitopes recognized by broadly neutralizing mAbs. The three gp120 monomers constituting the Env trimer are in shades of blue. The gp41 is in green. The 4E10 and 2F5 epitopes are not available until the Env has engaged its cellular receptors. 'CD4i Abs' and V3 loop Abs refer to the epitopes for CD4- and V3 loop-induced antibodies.
A study in South Africa has shown for the first time that **circumcising adult men** can dramatically lower their risk of becoming infected by HIV through heterosexual sex. Circumcision can offer 65% protection from infection. "It's essentially an anatomic vaccine for life."

The copy number of **CCL3L1** gene varies from person to person (due to segmental duplication) and influences an individual's level of the chemokine. But by itself, this number didn't determine HIV susceptibility. Rather, it depended on how many copies a person had compared to others of the same ancestry. For example, Africans have a median of four copies of **CCL3L1**, whereas Europeans have two. At first blush, this evidence seems to suggest that HIV might have a more difficult time causing harm in Africans. But a closer analysis revealed nothing of the sort.

There is no silver bullet, but both the researchers and evolution are busy working on the problem...
Genetic resistance to HIV via gene therapy

Approaches to modifying hematopoietic stem cells for HIV resistance
More than 2 million AIDS-related deaths occurred globally in 2008, and more than 33 million people are living with HIV/AIDS. Despite promising advances in prevention, an estimated 2.7 million new HIV infections occurred in that year, so that for every two patients placed on combination antiretroviral treatment, five people became infected. The pandemic poses a formidable challenge to the development, progress, and stability of global society 30 years after it was recognized. Experimental preventive HIV-1 vaccines have been administered to more than 44,000 human volunteers in more than 187 separate trials since 1987. Only five candidate vaccine strategies have been advanced to efficacy testing. The recombinant glycoprotein (rgp)120 subunit vaccines, AIDSVAX B/B and AIDSVAX B/E, and the Merck Adenovirus serotype (Ad)5 viral-vector expressing HIV-1 Gag, Pol, and Nef failed to show a reduction in infection rate. Most recently, a phase III trial that tested a heterologous prime-boost vaccine combination of ALVAC-HIV vCP1521 and bivalent rgp120 (AIDSVAX B/E) showed 31% efficacy in protection from infection among community-risk Thai participants.
Recommended reading


Albert Marquet
The Doll in the Window, 1935