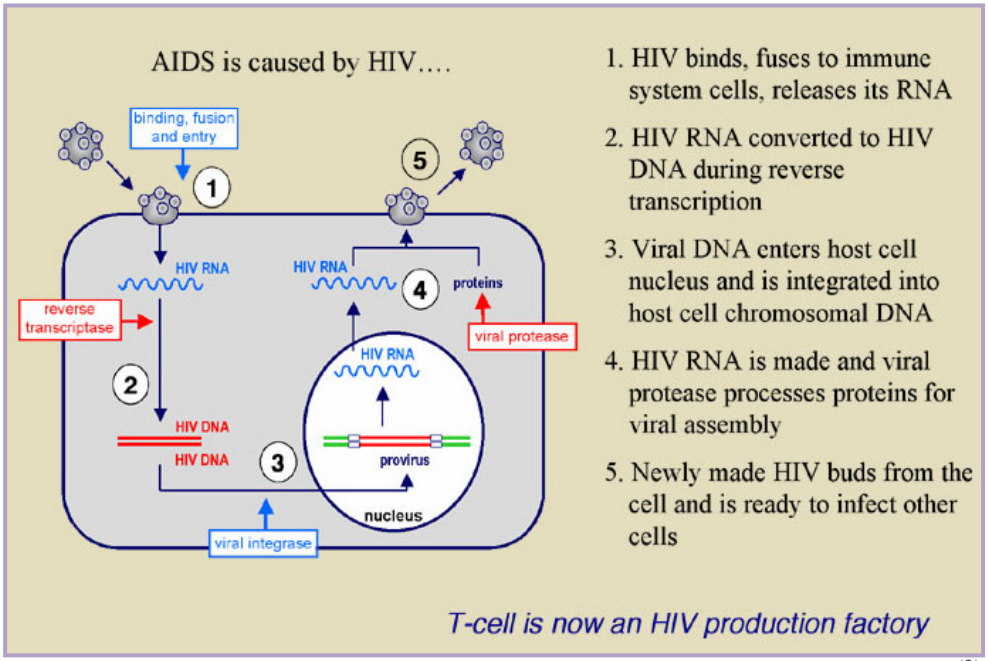
Antiretroviral Treatment for HIV

Treatment for HIV has improved significantly. When this disease began in the early 1980s, AIDS patients had few options. And although there is still no cure for AIDS, current therapies are able to inhibit the virus from replicating to reduce morbidity and death, giving patients longer and healthier lives.

Currently available drugs do not cure HIV infection or AIDS. They can suppress the virus, even to undetectable levels, but are unable to completely eliminate HIV from the body. Hence, infected patients still need to take antiretroviral drugs.

Antiretroviral drugs, also called antiviral drugs, for HIV are medication that interferes with the replication of retroviruses[1]. HIV is a retrovirus, so called because the virus' genetic material is made of RNA; the genetic material of humans is made of DNA. Illustrated below is a simple description of the HIV life cycle:



Source: Smith Lab Page, 2007 [2]

Types of Antiretroviral treatment for HIV

Antiviral drugs can be categorized into 3 main classes[3]:

(1) **Reverse transcriptase (RT) inhibitors**

These RT inhibitors interfere in a very important step in the HIV life cycle called reverse transcription. This step is where the viral RNA is converted to DNA which is crucial for replication of the virus. An enzyme known as reverse transcriptase is required for this step. There are two main types of RT inhibitors:

- Nucleoside/nucleotide RT inhibitors (NRTI) –

  These are similar to the building blocks used to make DNA except they are faulty. In the process in the process of converting RNA to DNA, the virus uses the faulty building blocks resulting in a halt the process and complete HIV DNA is not produced and the virus can't replicate.

  In 1987, Retrovir®, or AZT became the first antiretroviral to be approved. Interestingly, AZT was originally used for cancer treatment, although it failed efficacy tests and was associated with high side effects. Today, there are currently 13 FDA-approved NRTI drugs. These drugs work in a similar fashion.

Table 1. Current FDA-approved Nucleoside/nucleotide RT inhibitors (NRTI) drugs[4]

Brand Name	Generic Name(s)	Manufacturer
◦ Retrovir	azidothymidine (AZT); zidovudine (ZDV)	**GlaxoSmithKline**
◦ Videx	didanosine (ddI)	**Bristol Myers-Squibb**
◦ Videx EC	enteric coated didanosine (ddI EC)	**Bristol Myers-Squibb**
◦ Hivid	zalcitabine; dideoxycytidine (ddC)	**Hoffmann-La Roche**
◦ Zerit	stavudine (d4T)	**Bristol Myers-Squibb**
◦ Epivir	lamivudine (3TC)	**GlaxoSmithKline**
◦ Combivir	lamivudine + zidovudine	**GlaxoSmithKline**
◦ Ziagen	abacavir sulfate, ABC	**GlaxoSmithKline**
◦ Trizivir	abacavir + zidovudine + lamivudine	**GlaxoSmithKline**
◦ Viread	tenofovir disoproxil fumarate (TDF)	**Gilead**
◦ Emtriva	emtricitabine (FTC)	**Gilead Sciences**
◦ Epzicom	abacavir + lamivudine	**GlaxoSmithKline**
◦ Truvada	**tenofovir disoproxil fumarate + emtricitabine**	**Gilead Sciences, Inc.**

- Non-nucleoside RT inhibitors (NNRTI) –

  These bind to the enzyme reverse transcriptase and stop the virus from converting RNA to DNA.

  Viramune®, approved in 1996, was the first NNRTI. There are currently 3 FDA-approved NNRTI drugs.

Table 2. Current FDA-approved Non-nucleoside RT inhibitors (NNRTI) drugs[4]

Brand Name	Generic Name(s)	Manufacturer
◦ Rescriptor	delavirdine, DLV	**Pfizer**
◦ Sustiva	efavirenz, EFV	**Bristol Myers-Squibb**
◦ Viramune	**nevirapine, NVP**	**Boehringer Ingelheim**

(2) Protease inhibitors (PI)

Aside from the reverse transcriptase, HIV also use protease, another enzyme, to assemble new viral particles[5]. Protein inhibitors therefore interfere with the activity of protease. The first protease inhibitor, Invirase, was approved in 1995.There are currently 11 FDA-approved protease inhibitors for HIV treatment.

Table 3. Current FDA-approved Protease Inhibitors[4]		
Brand Name	**Generic Name(s)**	**Manufacturer**
◦ Agenerase	amprenavir, APV	**GlaxoSmithKline**
◦ Aptivus	tipranavir, TPV	**Boehringer Ingelheim**
◦ Crixivan	indinavir, IDV,	**Merck**
◦ Fortovase	saquinavir (no longer marketed)	**Hoffmann-La Roche**
◦ Invirase	saquinavir mesylate, SQV	**Hoffmann-La Roche**
◦ Kaletra	lopinavir and ritonavir, LPV/RTV	**Abbott Laboratories**
◦ Lexiva	Fosamprenavir Calcium, FOS-APV	**GlaxoSmithKline**
◦ Norvir	ritonavir, RTV	**Abbott Laboratories**
◦ Prezista	darunavir	**Tibotec, Inc.**
◦ Reyataz	atazanavir sulfate, ATV	**Bristol-Myers Squibb**
◦ Viracept	**nelfinavir mesylate, NFV**	**Agouron Pharmaceuticals**

(3) **Fusion Inhibitors**[6]

HIV infects human cells by being able to invade and enter human cells. The viral protein, GP41, is important for entry of virus into the cell. Fusion inhibitors works by binding the GP41 and prevents the virus from fusing with a cell's membrane and entry into the cells. Fuzeon®, FDA-approved in 2003, is currently the only fusion inhibitor.

Table 4. Current FDA-approved Fusion Inhibitors[4]		
Brand Name	Generic Name(s)	**Manufacturer**
◦ Fuzeon	**enfuvirtide, T-20**	**Hoffmann-La Roche & Trimeris**

Highly Active Antiretroviral Therapy (HAART)

Unfortunately, antiretrovirals are limited in their activity. When HIV replicates (i.e. makes new copies of itself) it often makes mistakes, thus creating different versions or strains HIV that may become resistant to antiretroviral drugs.

For antiretroviral treatment to be effective for a long time, it has been found that taking a combination of antiretroviral drug is better. In combination, the rate at which resistance develops is also greatly reduced.

The term Highly Active Antiretroviral Therapy refers to a strategy where a combination of three or more antiretroviral drugs is used for treatment. The combination includes at least drugs from two classes of antiretroviral drugs[3]. When used properly, the combination of drugs has been successful in HIV treatment by suppressing the virus and reducing the rate of opportunistic infections.

It should be noted that although HAART has greatly reduced the number of deaths due to HIV/AIDS, it has been thought to increase survival time by between 4 to 12 years[7]. However this strategy cannot suppress the virus completely and transmission of HIV can still occur. Adherence and commitment to a certain ARV or HAART regime is the best way to controlling HIV levels.

Side Effects of ARV Therapy

Most people take antiretroviral drugs have some side effect which can range from mild cases, such as fatigue and headache, to severe and sometimes fatal cases, such as liver damage[8,9]. Prescription drugs such as ARVs usually have a black box warning[10,11], sometimes called black label warning, which indicates that the drug carries significant risk of serious side effects or even life-threatening effects. Of course, the type of side effects a patient will experience will vary depending on how the body absorbs, metabolizes and breakdown the drugs. Higher amounts of drugs can also mean more side effects.

New Treatments

New antiretroviral drugs also targeting different stages in the HIV life cycle:

A. Entry inhibitor

This type of ARV prevents HIV from entering target cells, i.e. human CD4 cells. Entry into cell is facilitated by molecules on the surface of the target cells, known as co-receptors. One such co-receptor, CCR5[12], has been reported to be very important in HIV infection. Once HIV recognizes the CCR5, it binds to the cell via the co-receptor. It then fuses with the cell membrane to enter the cell.

There are a number of new experimental HIV drugs designed to interfere with the interaction between HIV and CCR5, including:

Experimental drug	Manufacturer
◦ **PRO140**	**Progenics**
◦ **Vicriviroc**	**Schering Plough**
◦ **Aplaviroc**	**GlaxoSmithKline**
◦ **Maraviroc**	**Pfizer**

While CCR5 is a major co-receptor by which HIV infects cells, other co-receptors do exist. There are also experimental drugs targeting the interaction between another coreceptor, CXCR4[13], and HIV:

Experimental drug	Manufacturer
◦ **AMD-070**	**Genzyme Corporation**
◦ **TNX-355**	**Tanox Biosystem**
◦ **BMS-488043**	**Bristol-Myers Squibb**

B. Integrase inhibitor[14]

This class of antiretroviral drug target a HIV enzyme known as integrase. During HIV's lifecycle, after the reverse transcriptase enzyme has converted the single stranded viral RNA to double stranded DNA, the DNA is inserted, or integrated, into the DNA of the infected cell, i.e. human CD4 cells. This is done with the assistance of the integrase enzyme. This makes it possible for the infected cell to make new copies of HIV. By interfering with integrase, integrase inhibitors prevent HIV genetic material from integrating in the target cell, thus stopping viral replication.

No integrase inhibitors have yet received governmental approval, although two are currently undergoing testing:

Experimental drug	Manufacturer
◦ **MK-0518**	**Merck**
◦ **GS-9137**	**Gilead**

C. Maturation inhibitor[9]

Maturation is the last step in the HIV life cycle, in which the virus "grows up" to become infectious. Maturation inhibitors aim to prevent HIV from properly assembling and maturing, from forming a protective outer coat, or from emerging from human cells. Inhibiting this step is an entirely new way to halt or inhibit HIV replication.

Currently there are no FDA approved maturation inhibitors available. There is one maturation inhibitor in trials currently:

Experimental drug	Manufacturer
◦ **PA-457**	**Panacos**

PA-457 or Bevirimat as it has been named is from the drug manufacturer Panacos[15]. Bevirimat blocks HIV maturation by inhibiting the final step in the processing of a HIV protein. The resulting virus particles are structurally defective and are incapable of spreading infection around the body.

References

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