

# HUMAN IMMUNODEFICIENCY VIRUS (HIV) DISEASE ANTIRETROVIRAL THERAPY IN HIV

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**ABSTRACT :** The advent of highly active antiretroviral therapy (HAART) has led to a significant decline in HIV-associated morbidity and mortality. Despite these recent advances, the majority of patients with HIV/AIDS worldwide are still lacking access to treatment. To date, there are 21 approved antiretrovirals divided into four categories based on their mechanism of action. We review the basic characteristics of these antiretrovirals. We also briefly discuss current guidelines regarding the use of antiretrovirals in general as well as in special populations such as in pregnant women, in occupational exposure and non occupational exposure.

The treatment for infection by the human immunodeficiency virus has undergone major developments in the last decade. Currently, the Food and Drug Administration (FDA) has approved 21 different antiretroviral drugs and four co-formulated products. These drugs are subdivided into four categories : nucleoside/nucleotide analogue reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, and fusion inhibitors (Table I).

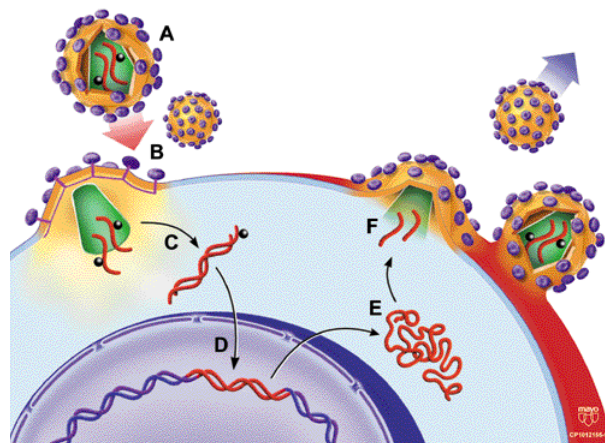
A brief review of the HIV replication cycle will assist in understanding the mechanisms of actions of antiretrovirals (Figure 1) [1]. HIV is an enveloped virus containing two copies of viral genomic RNA and transfer RNA in its core in addition to *gag* and *pol* protein products. The envelope proteins of the virus interact with CD4 receptors and co-receptors of the host cell, leading to fusion of the viral envelope and host cell membrane. The viral RNA enters the host cell and is converted into DNA by the viral reverse transcriptase. The viral DNA then integrates into the host DNA. Subsequently, the viral genes are transcribed to produce viral proteins, such as the precursor Gag and Gag-Pol proteins, which are used to assemble new viral particles. Protease enzyme cleaves the precursor Gag and Gag-Pol proteins into their final products.

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- A. The interaction between the envelope proteins of the virus and CD4 receptor and coreceptors of the host cell leads to the binding of the viral envelope and the host cytoplasmic membrane.
- B. The viral reverse transcriptase enzyme catalyzes the conversion of viral RNA into DNA.
- C. The proviral DNA enters the nucleus and becomes integrated into the chromosomal DNA of the host cell. This process is catalyzed by the viral enzyme integrase.
- D. Expression of the viral genes leads to production of viral RNA and proteins.
- E. The protease enzyme cleaves the precursor *gag* and *gag-pol* proteins into functional mature products.
- F. Viral proteins as well as viral RNA are assembled at the cell surface into new viral particles and leave the host cell by a process called budding. During the process of budding, they acquire the outer layer and envelope.

FIGURE 1. Simplified schema of HIV-1 life cycle  
(Plate 12-2 from Chapter 12, Temesgen, Z. *HIV Infection*.  
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## ANTIRETROVIRAL DRUGS

### Nucleoside analogue reverse transcriptase inhibitors (NRTIs)

Nucleoside analogue reverse transcriptase inhibitors structurally resemble the building blocks of DNA and RNA, but differ by the replacement of the hydroxyl group in the 3' position by another group unable to form the 5' to 3' phosphodiester linkage needed for DNA elongation. NRTIs compete with the natural nucleotides and block reverse transcriptase activity. After phosphorylation by cellular kinases, the NRTIs are incorporated into viral DNA and act as chain terminators in the synthesis of proviral DNA. Characteristics of the currently available NRTIs are shown in Table II.

**TABLE I**  
**CURRENT ANTIRETROVIRAL MEDICATIONS\***

NRTI/NtRTI		NNRTI	PI		FUSION INHIBITORS		
Zidovudine	(ZDV)	Nevirapine	(NVP)	Saquinavir	(SQV)	Enfuvirtide	(T-20)
Didanosine	(ddl)	Delavirdine	(DLV)	Indinavir	(IDV)		
Zalcitabine	(ddC)	Efavirenz	(EFV)	Ritonavir	(RTV)		
Stavudine	(d4T)			Nelfinavir	(NFV)		
Lamuvudine	(3TC)			Amprenavir	(APV)		
Abacavir	(ABC)			Lopinavir/r	(LPV/r)		
Tenofovir	(TDF)			Atazanavir	(ATV)		
Emtricitabine	(FTC)			Fosamprenavir	(FPV)		
Combivir	(COM)			Tipranavir	(TPV)		
Trizivir	(TZV)						
Truvada							
Epzicom							

\* **NRTI** : nucleoside analogue reverse transcriptase inhibitor **NtRTI** : nucleotide analogue reverse transcriptase inhibitor  
**NNRTI** : nonnucleoside reverse transcriptase inhibitor **PI** : protease inhibitor

### Nonnucleoside reverse transcriptase inhibitors (NNRTIs)

Nonnucleoside reverse transcriptase inhibitors operate by a separate mechanism. NNRTIs bind noncompetitively to a different site on the reverse transcriptase from the usual nucleotide substrate site. This causes a conformational change in the reverse transcriptase that blocks its enzymatic activity. As opposed to the NRTIs, the NNRTIs do not require intracellular phosphorylation to be active. Characteristics of the currently available NNRTIs are shown in Table III. Many NNRTIs are metabolized by the cytochrome P-450 system and, therefore, can have significant drug-drug interactions.

### Protease inhibitors (PIs)

The protease inhibitors represent a third class of antiretroviral agents. These drugs act by inhibiting HIV-1 protease. The action of this enzyme is to cleave the large viral *gag* and *gag-pol* polypeptide chains into smaller functional proteins. This allows for the formation of the infectious HIV virion. By inhibiting HIV-1 protease, the virions produced are structurally disorganized and noninfectious. Protease inhibitors have antiviral activity in both acutely and chronically infected cells. Also, the protease inhibitors are metabolized by the cytochrome P-450 system and can have significant interactions with other drugs metabolized by this system. Characteristics of the currently available PIs are shown in Table IV.

### Fusion inhibitors

The newest class of antiretroviral agents to be approved for the treatment of HIV infection is the class of fusion inhibitors. Currently, there is only one fusion inhibitor, Enfuvirtide (T-20 or Fuzeon®), approved by the FDA. It is a linear 36-amino acid synthetic peptide composed of

naturally occurring L-amino acid residues. It interferes with the entry of HIV-1 into cells by inhibiting fusion of viral and cellular membranes. It binds to the gp41 subunit of the viral envelope glycoprotein and prevents the conformational changes required for the fusion of viral and cellular membranes [2].

Enfuvirtide is available in an injectable form and is given twice a day. The oral bioavailability is 84.3% and the serum half-life is 3.8 hours. Common adverse effects include local injection site reactions, increased bacterial pneumonia, and rarely, hypersensitivity reactions (< 1%).

### GUIDELINES FOR USE OF ANTIRETROVIRAL THERAPY FOR HIV INFECTION

Guidelines are available to address the issues of antiretroviral therapy in specific populations. The guidelines for treatment of HIV infection in the general population, pregnancy, perinatal period, and post-exposure prophylaxis are discussed below.

### Guidelines for use of antiretroviral agents in HIV-infected adults

Current recommendations for treatment of HIV-infected adults and adolescents have been developed by a panel of leading AIDS specialists, convened by the Department of Health and Human Services (DHHS) in collaboration with the Henry J. Kaiser Family Foundation [3]. The primary goals of therapy are to reduce HIV-related morbidity and mortality, improve the quality of life, restore and preserve immunologic function, and maximally and durably suppress viral load. Antiretroviral therapy is recommended for those individuals with acute HIV syndrome, those who are within six months of seroconversion, and those with symptoms secondary to HIV infection.

The initiation of antiretroviral therapy in asymp-

**TABLE II**  
GENERAL CHARACTERISTICS OF CURRENTLY AVAILABLE  
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

NRTI	DOSE	BIOAVAILABILITY	PROTEIN BINDING	CSF PENETRATION*	MAJOR ADVERSE EFFECTS	FOOD EFFECTS
<b>Abacavir</b>	300 mg b.i.d. (in <i>Trizivir</i> ® 1 tablet b.i.d.) (in <i>Epzicom</i> ® 1 tablet once daily)	> 80%	50%	27-33%	Hypersensitivity reactions	No significant effect**
<b>Didanosine</b>	200mg b.i.d. OR 400 mg once daily	30-40%	< 5%	20%	Pancreatitis Peripheral neuropathy	Take on empty stomach
<b>Emtricitabine</b>	200 mg once daily (in <i>Truvada</i> ® 1 tablet once daily)	93%	50-95%	4%	Minimal	No significant effect
<b>Lamivudine</b>	150 mg b.i.d. (in <i>Combivir</i> ® 1 tablet b.i.d.) (in <i>Epzicom</i> ® 1 tablet once daily) (in <i>Trizivir</i> ® 1 tablet b.i.d.)	> 80%	< 36%	5.6-30.9%	Minimal	No significant effect
<b>Stavudine</b>	40 mg b.i.d.	> 80%	Negligible	40%	Peripheral neuropathy	No significant effect
<b>Tenofovir</b>	300 mg once daily	25-39%	25%	NA	Asthenia. Headache Gastrointestinal, renal insufficiency	No significant effect
<b>Zalcitabine</b>	0.75 mg t.i.d.	80%	< 4%	9 -37%	Peripheral neuropathy Oral ulcers	No significant effect
<b>Zidovudine</b>	300 mg b.i.d. OR 200 mg t.i.d.	65%	24-28%	53%	Bone marrow suppression	No significant effect

\* As percent of concurrent serum levels    \*\* No significant effect means drug can be taken without regards to food  
b.i.d. : twice daily    t.i.d. : three times daily    NA : not available

**TABLE III**  
GENERAL CHARACTERISTICS OF CURRENTLY AVAILABLE  
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

NNRTI	DOSE	BIOAVAILABILITY	PROTEIN BINDING	CSF PENETRATION*	MAJOR ADVERSE EFFECTS	FOOD EFFECTS	EFFECTON P450
<b>Efavirenz</b>	600 mg daily	Unknown	99.5-99.75%	0.26-1.19%	Rash. CNS symptoms Fetal malformations in primates	Avoid high fat meals	Induction & inhibition
<b>Delivardine</b>	400 mg t.i.d.	> 80%	98%	< 1%	Rash	No significant effect**	Inhibition
<b>Nevirapine</b>	200 mg b.i.d.	90%	60%	45%	Rash	No significant effect	Induction

\* As percent of concurrent serum levels    \*\* No significant effect means drug can be taken without regards to food    b.i.d. : twice daily    t.i.d. : three times daily

omatic HIV-infected individuals remains debatable. The decision to treat asymptomatic individuals depends upon the patient's willingness to begin therapy, degree of existing immunodeficiency (as determined by the CD4<sup>+</sup> T cell count), risk of disease progression (as determined by the CD4<sup>+</sup> T cell count and HIV RNA load), potential benefits and risks of therapy, and likelihood of adherence to the treatment regimen. In general, the DHHS panel recommends initiating therapy for all symptomatic individuals or asymptomatic individuals with a CD4 cell

count < 200 cells/mm<sup>3</sup>, regardless of the viral load. Although the data is inconsistent, some clinicians consider treatment when the CD4 count drops < 350 cells/mm<sup>3</sup> and HIV-RNA load is > 100,000 copies/mL (Table V).

Treatment response is evaluated by following plasma HIV RNA (viral load) levels at baseline and every 3 to 4 months, or more frequently if warranted by the clinical scenario. A minimal change in plasma viremia is considered to be a threefold or 0.5-log<sub>10</sub> increase or decrease. For therapy failures, a new regimen can be chosen that

consists of at least two new agents without cross-resistance to the drugs in the failed regimen. Resistance testing (genotyping and/or phenotyping) can be useful in making the appropriate drug choices for a subsequent treatment regimen.

### Recommendations for use of antiretroviral drugs in pregnant women

In 1994, the Pediatric AIDS Clinical Trial Group Protocol 076 demonstrated that a three-part regimen of zidovudine (ZDV) administered to the mother and newborn was able to reduce the perinatal transmission of HIV by two-thirds [4]. The treatment regimen consisted of oral ZDV initiated at 14-34 weeks of gestation and continued throughout the pregnancy, followed by intravenous ZDV during labor and oral administration of ZDV to the newborn for 6 weeks. Due to this study, the U.S. Public Health Service recommended universal prenatal HIV counseling and testing with consent for all pregnant women and the use of zidovudine for reduction of perinatal HIV transmission [5]. Since then, there has been a dramatic decrease in perinatal HIV transmission.

The treatment of pregnant HIV-infected women has two separate but related aims : treatment of the mother

and reduction of transmission to the fetus. Benefits of therapy must also be weighed against the potential adverse effects on the fetus or newborn. Antiretroviral therapy should be offered to all HIV-1 infected women during pregnancy. The choice of antiretroviral therapy for pregnant woman should take into consideration the possible changes in dosing requirements resulting from physiologic changes of pregnancy, potential effects of antiretroviral drugs on the pregnant woman, and the potential short and long-term effects of the drug on the fetus and newborn. The potential harm of a specific drug depends on the particular dosage, gestational age of the fetus at exposure, duration of exposure, and interaction with other agents to which the fetus is exposed. Data regarding the teratogenicity, mutagenicity, and carcinogenicity are limited for antiretroviral drugs, especially when used in combination therapy. Therefore, the choice of therapy must be individualized and based on discussion with the woman and available data.

### Recommendations for occupational postexposure prophylaxis

Current evidence shows that the average risk for HIV transmission is approximately 0.3% after percutaneous

**TABLE IV**  
GENERAL CHARACTERISTICS OF CURRENTLY AVAILABLE PROTEASE INHIBITORS (PIs)

PI	DOSE	BIOAVAILABILITY	PROTEIN BINDING	ADVERSE EFFECTS	FOOD EFFECTS	P450 INHIBITION
<b>Amprenavir</b>	1400 mg b.i.d.	60-80%	90%	Gastrointestinal Rash Paresthesias	With or without but avoid high fat meals	++
<b>Atazanavir</b>	400 mg once daily	High, but unable to quantify	85%	Hyperbilirubinemia Prolonged PR interval Hyperglycemia	With meals	++
<b>Fosamprenavir</b>	1400 mg b.i.d. OR 700 mg b.i.d. with RTV	NA	90%	Rash Gastrointestinal Headache	No significant effect*	++
<b>Indinavir</b>	800 mg q 8 hr	60%	60%	Gastrointestinal Nephrolithiasis Hyperbilirubinemia	On empty stomach or with light snack	++
<b>Lopinavir (+ Ritonavir)</b>	3 capsules b.i.d.	NA	98-99%	Gastrointestinal Weakness Headache Hyperbilirubinemia	With meals	++++
<b>Nelfinavir</b>	750 mg t.i.d.	20-80%	> 98%	Diarrhea	With meals	++
<b>Ritonavir</b>	600 mg b.i.d.	75%	98-99%	Gastrointestinal Paresthesia Taste perversion (liquid)	With meals	++++
<b>Saquinavir (Fortovase)</b>	1200 mg t.i.d.	12%	98%	Gastrointestinal	With fatty snacks or full meal	+

\* No significant effect means drug can be taken without regards to food    **b.i.d.** : twice daily    **t.i.d.** : three times daily    **NA** : not available

exposure to HIV-infected blood [6] and 0.09% after mucous membrane exposure [7]. HIV transmission after non-intact skin exposure has not been precisely quantified, but estimated to be lower than the risk for mucous membrane exposure. The risk for transmission after exposure to fluids or tissues, other than blood, has also not been quantified, but is likely to be considerably lower than for blood exposures. Several factors affect the risk of HIV transmission. The risk for infection increased with exposure to a larger quantity of HIV-infected blood, such as via hollow-bore needles or deeper injuries. The risk of transmission was also higher after exposure to blood from persons with terminal illness, possibly related to a higher viral load in blood late in the course of AIDS.

A retrospective case-control study of health care workers with percutaneous exposure to HIV documented that the use of zidovudine was associated with a 79% decrease in the risk of transmission [8]. Results of that study, as well as results from studies in animals and data from the Pediatric AIDS Clinical Trial Group on the efficacy of zidovudine for preventing perinatal transmission of HIV, prompted the U.S. Public Health Service to issue recommendations for prophylaxis in health care workers after occupational exposure to HIV.

With the availability of new drugs and the accumulation of more knowledge, these 1996 guidelines have recently been updated [9]. The guidelines provide an algorithm to guide clinicians in assessing risk and deciding when to offer postexposure prophylaxis. Systems, including written protocols, should be in place to prompt reporting and facilitate management of exposed health care workers. For most HIV exposures, a four-week regimen of two antiretroviral drugs (zidovudine and lamivudine) is recommended. The addition of a protease inhibitor is recommended for exposures with an increased risk of transmission or when resistance to one of the recommended drugs is known or suspected. Individual clinicians may, of course, prefer other antiretroviral drugs or combinations because of local knowledge and experience.

### Recommendations for non-occupational postexposure prophylaxis

The U.S. Department of Health and Human Services (DHHS) Working Group on Non-occupational Postexposure Prophylaxis (nPEP) has made the following recommendations [10]. A 28-day course of highly active antiretroviral therapy (HAART) is recommended for persons seeking care > 72 hours after non-occupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person known to be HIV infected, when that exposure represents a substantial risk for transmission. Antiretroviral medications should be started as soon as possible after exposure for the best chance of success.

For persons seeking care > 72 hours after non-occupational exposure to potentially infectious body fluids of

TABLE V

### Indications for Antiretroviral Therapy\*

- Antiretroviral therapy is recommended for all patients with history of an AIDS-defining illness or severe symptoms of HIV infection regardless of CD4<sup>+</sup> T cell count.
- Antiretroviral therapy is also recommended for asymptomatic patients with < 200 CD4<sup>+</sup> T cells/mm<sup>3</sup>.
- Asymptomatic patients with CD4<sup>+</sup> T cell counts of 201-350 cells/mm<sup>3</sup> should be offered treatment.
- For asymptomatic patients with CD4<sup>+</sup> T cell of > 350 cells/mm<sup>3</sup> and plasma HIV RNA > 100,000 copies/mL, most experienced clinicians defer therapy, but some clinicians may consider initiating treatment.
- Therapy should be deferred for patients with CD4<sup>+</sup> T cell counts of > 350 cells/mm<sup>3</sup> and plasma HIV RNA < 100,000 copies/mL.

\*From the *DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, October 6, 2005.

a person with unknown HIV status, and when such exposure would represent a substantial risk for transmission if the source were HIV infected, the DHHS makes no specific recommendations for or against the use of nPEP. Instead, clinicians should evaluate the risks and benefits of treatment on a case-by-case basis.

Lastly, the DHHS does not recommend the use of nPEP for persons with exposure histories that represent no substantial risk for HIV transmission or who seek care > 72 hours after exposure. However, clinicians may consider prescribing nPEP for exposures conferring a serious risk for transmission, even if the person seeks care > 72 hours after exposure if, in their judgment, the diminished potential benefit of nPEP outweighs the risks for transmission and adverse events. In addition, risk-reduction counseling and indicated intervention services should be provided to reduce the risk for recurrent exposures.

### CONCLUSION

These recommendations are based on information available at the time they were developed. A mechanism has been put in place, through the HIV/AIDS Treatment Information Service Web site (<http://www.aidsinfo.nih.org>), to regularly refine and update the recommendations in tandem with the evolution of knowledge about HIV infection.

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