

# Human Immune Deficiency Virus-1: Diagnosis and Treatment in Adults and Adolescents

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## Introduction

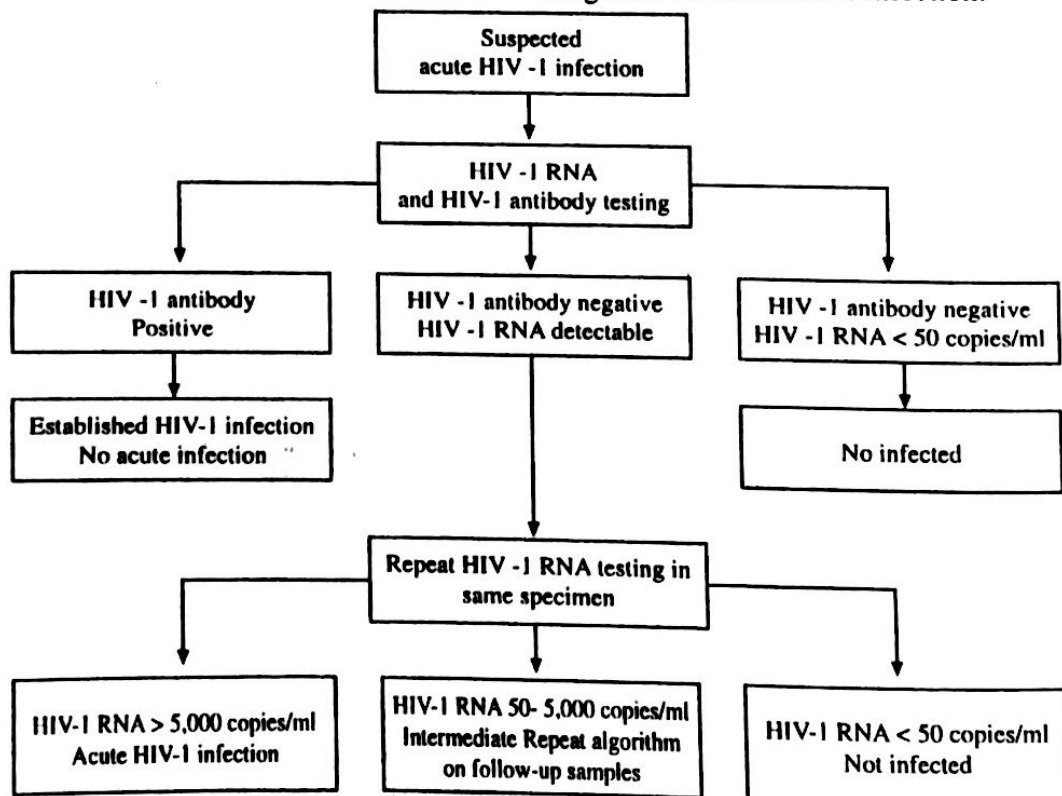
Acute HIV-1 infection presents in 40 - 90 % of cases as a transient symptomatic illness, associated with high levels of HIV-1 replication and an expansive virus-specific immune response. With 14,000 new cases per day worldwide, it is an important differential diagnosis in cases of fever of unknown origin, maculopapular rash and lymphadenopathy.

## Diagnosis

The diagnosis of acute HIV-1 infection is based on the detection of HIV-1 replication in the absence of HIV-1 antibodies, as these are not yet present at this early stage of infection. Different tests are available for diagnosis of acute HIV-1 infection. The most sensitive tests are based on detection of plasma HIV-1 RNA.

The diagnosis of acute infection is missed in the majority of cases, as other viral illnesses ("flu") are often assumed to be the cause of the symptoms, and there are no HIV-1-specific antibodies detectable at this early stage of infection. The diagnosis therefore requires a high degree of clinical suspicion, based on clinical symptoms and history of exposure, in addition to specific laboratory tests (detection of HIV-1 RNA or p24 antigen and negative HIV-1 antibodies) confirming the diagnosis.

The only test licensed for earlier detection of HIV-1 infection is the serum or plasma p24 antigen test, which is used routinely in blood donors to detect viral infection before the development of HIV-1 antibodies. Cases of acute HIV-1 infection have also been accurately diagnosed on the basis of high plasma viral RNA levels. The detection of high-titer viral RNA or viral p24 antigen in a patient with a negative test for HIV-1 antibodies establishes the diagnosis of acute HIV-1 infection.



Algorithm showing HIV infection and confirmation

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Testing for HIV antibodies invariably necessitates the availability of at least two different assays:

1. A screening test and
2. A confirmatory test.

Most screening tests are based on the ELISA principle (enzyme linked immuno sorbent assay) Screening tests must be extremely sensitive to minimize the chance of yielding a false-negative.

If the result of such a screening test is positive, this has to be confirmed by at least one confirmatory assay. For this purpose, some countries such as Germany and the United States prescribe the use of a so-called Western blot or immunofluorescence assay (IFT or IFA).

### Test results

False-positive results by Western blot are very rare. A positive Western blot result therefore confirms the presence of HIV-specific antibodies and thus, HIV infection.

A positive test result (i.e. screening and confirmatory tests positive) is infected with HIV (i.e. carries the virus that causes AIDS).

- a. May infect others with HIV unless precautions are taken.
- b. A positive test result does NOT mean that the person tested
  - (i) has AIDS;
  - (ii) will necessary develop AIDS.
- c. A negative test result means:
  - (i) HIV antibodies were not detected in the blood of the individual at the point in time when he or she was tested.
- d. A negative test result does NOT mean that:
  - (i) the individual is not infected with HIV (the test could have been performed during the "diagnostic window" period);
  - (ii) the person tested is immune or resistant to HIV;
  - (iii) the person tested can have sexual intercourse without taking "safe sex" precautions.

Beyond the "diagnostic window", meaning later than six months after a possible exposure to HIV, an HIV screening test is rarely "false-negative". Therefore, a negative test means that the person is

not infected with HIV - always assuming of course that in the meantime no renewed exposure has taken place.

### WHO Clinical Staging of HIV Infection

#### Stage I

- a. Asymptomatic
- b. Persistent generalized lymphadenopathy
- c. Performance scale I – asymptomatic, normal acvtivity

#### Stage II

- a. Weight loss < 10 % of body weight
- b. Minor mucocutaneous manifestation (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulceration and angular cheilitis)
- c. Herpes zooster in last five years
- d. Recurrent upper respiratory tract infections (e.g. Bacterial sinusitis) and or performance scale 2 – symptomatic, normal activity.

#### Stage III

- a. Weight loss > 10% of body weight
- b. Unexplained chronic diarrhoea > 1 month
- c. Unexplained prolong fever (intermittent or continuos ) >1 month
- d. Oral candidiasis
- e. Oral hairy leukoplakia
- f. Pulmonary tuberculosis within past year
- g. Severe bacterial infections (e.g. pneumonia, pyomyositis) and or performance scale 3- bed ridden < 50% of the day during the last month

#### Stage IV

- a. HIV wasting syndrome
- b. Pneumocystic carinii pneumonia
- c. Toxoplasmosis of the brain
- d. Cryptosporidiosis, extrapulmonary
- e. Cytomegalovirus disease of an organ other than liver, spleen or lymph node
- f. Herpes simplex virus infection , mucocutaneous > 1 month or visceral of any duration

- g. Progressive multifocal leukoencephalopathy
- h. Any disseminated endemic mycosis (e.g. histoplasmosis, coccidioidomycosis) candidiasis of oesophagus, trachea, bronchi or lungs
- i. Atypical mycobacteriosis disseminated
- j. Non typhoid salmonella septicaemia
- k. Extra pulmonary tuberculosis
- l. Lymphoma
- m. Kaposi sarcoma
- n. HIV encephalopathy Performance scale 4- bed ridden > 50 % of the day during the last month.

## Treatment

### Indication for Antiretroviral therapy

- a. WHO stage IV irrespective of CD4 cell count
- b. WHO stage III disease treat, but consider CD4 values for better management and decision making in some situation (e.g. TB )
- c. WHO stage I or II disease with CD4 cell counts less than 200/mm<sup>3</sup> ( consider treatment if closer to 200- 250 )

Consensus guidelines support the strategy of offering antiretroviral therapy to anyone with HIV-related symptoms or signs. Although data from randomized trials are not sufficient to guide the decision regarding when to initiate antiretroviral therapy in asymptomatic persons, several observational cohort studies have provided useful information. The near-uniform finding that disease progression and mortality are significantly worse among patients whose treatment is delayed until the CD4 cell count is less than 200 per cubic millimeter indicates that antiretroviral therapy should be initiated when the CD4 cell count is above this level. Persons who present initially with CD4 cell counts of less than 200 cells per cubic

millimeter should be offered treatment as soon as the baseline evaluation and initial counseling regarding drug adherence are completed. Persons with CD4 cell counts of more than 350 per cubic millimeter generally can be observed without therapy, on the basis of data showing similar outcomes with and without therapy among patients with CD4 cell counts in this range exceptions are patients whose plasma HIV-1 RNA level is more than 100,000 copies per milliliter, since this level is associated with an increased risk of progression to AIDS that is independent of the CD4 cell count. In persons who are being followed without therapy, a rapid decline in the CD4 cell count (i.e., a decline of more than 100 cells per cubic millimeter per year) may also be factored into the decision regarding when to initiate therapy.

For persons with CD4 cell counts between 200 and 350 per cubic millimeter, the recommendation to start therapy should be considered on an individual basis. In practical terms, initiating antiretroviral therapy when the CD4 cell count is at the upper end of this range is reasonable if the patient is willing and committed. This strategy provides a buffer by which to avoid a drop in the CD4 cell count to less than 200 cells per cubic millimeter and may also prevent symptomatic disease, which can occur above this cutoff. One study has suggested that a level within the range of 200 to 350 cells per cubic millimeter, and specifically of about 275 cells per cubic millimeter, may be a threshold below which progression to AIDS is more likely.

### Antiretroviral drugs:

#### Nucleoside/Nucleotide reverse transcriptase inhibitors ( NRTIS )

1. Emtricitabine FTC
2. Lamivudine 3TC

3. Zalcitabine ddC
4. Zidovudine AZT
5. Didanosine ddI
6. Tenofovir TDF
7. Stavudine d4T
8. Abacavir ABC

3. Saquinavir soft gel SQV-FTV
4. Saquinavir hard gel SQV-INV
5. Lopinavir/ritonavir LPV
6. Fosamprenavir FPV
7. Ritonavir RTV
8. Atazanavir ATV
9. Nelfinavir NFV

**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

1. Delavirdine DLV
2. Efavirenz EFV
3. Nevirapine NVP

**Protease Inhibitors (PIs)**

1. Amprenavir APV
2. Indinavir IDV

**Fusion inhibitors**

1. Enfuvirtide T-20

Selection Initial Antiretroviral Regimens and Components for HIV-Infected Patients with Drug-susceptible Virus.ϕ

**A Nonnucleoside Reverse-Transcriptase Inhibitor plus Two Nucleoside (or one Nucleoside and One Nucleotide) Reverse-Transcriptase Inhibitors.λ**

	<b>NNRTI Component</b>	<b>Alternative NNRTI Component</b>	<b>NRTI Components</b>	<b>Alternative NRTI Component</b>
<b>Examples</b>	Efavirenz (Sustiva): 600 mg once daily	Nevirapine (Viramune): 200 mg once daily for 14 days, then 200 gm twice daily.	Zidovudine-lamivudine (Epzicom): 300mg and 150 mg twice daily as fixed dose combination; or tenofovir-emtricitabine (Truvada): 300mg and 200 mg once daily as fixed-dose combination.	Abacavir-lamivudine (Epzicom): 600 mg and 300 mg once daily as fixed dose combination.
<b>Major side effects</b>	Efavirenz: central nervous system (e.g., vivid dream); rash; hepatotoxicity; teratogenic effects in first trimester.Ψ	Nevirapine: rash, hepatotoxicity, hypersensitivity syndrome; should be used with caution in women and men with CD4 cell counts of >250/mm <sup>3</sup> and >400/mm <sup>3</sup> , respectively, because of increased risk of hepatotoxicity	Zidovudine (Retrovir) ♦: headache, nausea, anemia, leukopenia; tenofovir (Viread) ♦: gastrointestinal symptoms, renal dysfunction; lamivudine (EpiVir) and emtricitabine (Emtriva) ♦: generally well tolerated	Abacavir (Zigagen) ♦: 5% incidence of hypersensitivity syndrome (fever, rash, gastrointestinal symptoms, respiratory symptoms), which may be fatal, especially on rechallenge

**A Protease Inhibitor plus Two Nucleoside (or One Nucleoside and One Nucleotide)  
Zidovudine (Retrovir) λ**

	<b>PI Component</b>	<b>Alternative PI Component †</b>	<b>NRTI Components</b>	<b>Alternative NRTI Component</b>
<b>Examples</b>	Lopinavir-ritonavir (kaletra): 400mg and 100mg twice daily or 800mg and 200 mg once daily as fixed-dose combination	Atazanavir-ritonavir (Reyataz and Norvir): 300mg and 100mg once daily	Zidovudine-lamivudine: 300mg and 150mg twice daily as fixed-dose combination; or tenofovir-emtricitabine: 300mg and 200mg once daily as fixed-dose combination	Abacavir-lamivudine : 600 mg and 300 mg once daily as fixed dose combination.
<b>Major side effects</b>	Lopinavir-ritonavir: gastrointestinal symptoms; elevated liver-enzyme levels; hyperlipidemia; fat redistribution; insulin resistance	Atazanavir: increased indirect bilirubin levels; gastrointestinal symptoms; prolonged PR interval	Zidovudine ♦ headache, nausea, anemia, leukopenia; tenofovir ♦ (Viread): gastrointestinal symptoms, renal dysfunction; can lower atazanavir levels unless latter is administered with low dose ritonavir; lamivudine and emtricitabine ♦: generally well tolerated.	Abacavir ♦ : 5% incidence of hypersensitivity syndrome (fever, rash, gastrointestinal symptoms, respiratory symptoms), which may be fatal, especially on rechallenge

♦The regimens listed in this table were chosen to illustrate the selection of components of drug combinations that based on nonnucleoside reverse-transcriptase inhibitors (NNRT) and protease inhibitors (PI). Efficacy, toxicity, and simplicity of the regimens as demonstrated in clinical trials formed the basis of selection. This table is not intended to be comprehensive with respect to all possible initial combinations or to be a substitute for consensus guidelines; however, the regimens listed are concordant with these guidelines, NRTI denotes nucleoside or nucleotide reverse-transcriptase inhibitor. Data are from the Department of Health and Human Services<sup>12</sup> and Yeni et al.<sup>17</sup>

λ Multiple drug interactions occur with nonnucleoside reverse transcriptase inhibitors and protease inhibitors because of their metabolism by, and influence on, the CYP3A4 hepatic-enzyme system. All HIV non- HIV medications prescribed for patients who take these drugs should be checked for possible interaction. Decreased bone mineral density in women and men may occur as a side

effect of protease inhibitors or tenofovir as a manifestation of underlying HIV disease or both.

Ψ Because of the potential of teratogenic effects, efavirenz is contraindicated during the first trimester of pregnancy and in women with child bearing potential who are not using effective contraception.

♦ All nucleoside or nucleotide reverse-transcriptase inhibitors carry a warning label concerning the risk of mitochondrial dysfunction, steato-hepatitis, and lactic acidosis, which can be fatal. The risk varies among the drugs in this class; tenofovir, lamivudine, emtricitabine and abacavir have a lower risk, in relative terms, than doses stavudine (Zerif). The former also confer a lower risk of lipodystrophy than doses stavudine.

† Other alternative protease inhibitor components include saquinavir (Invirase)- ritonavir 1000 mg and 100 mg twice daily and fosamprenavir (Lexiva)-ritonavir, 700mg and 100 mg twice daily or 1400 mg and 200 mg once daily.



**Primary Prophylaxis against Major infection pathogens That Can Causes Complications in the Patient with Newly Diagnosed HIV infection. ☆**

Pathogen	CD4 Count (cells/mm <sup>3</sup> )	Agent	Major Side Effects	Alternative Agent
Pneumocystis jiroveci	<200	Trimethoprim-sulfamethoxazole 160 mg and 800 mg, once daily.	Rash, fever, abnormal liverenzyme levels, hematologic toxicity, pancreatitis.	Dapsone, 100 mg once daily (if G6PD level is normal)
Taxoplasma gondii	<100	Trimethoprim-sulfamethoxazole, 160 mg and 800 mg, once daily.	Rash, fever, abnormal liverenzyme levels, hematologic toxicity, pancreatitis.	Dapsone 200 mg, plus pyrimethamine 75 mg, plus leucocorin 25 mg, once weekly.
Mycobacteriuavium complex	<50	Azithromycin 1200 mg, once weekly	Gastrointestinal symptoms	Clarithromycin 500 mg, twice daily.
M.tuberculosis	Any (tuberculin skin test, positive at in-duration of > 5 mm, or history of significant exposure)	Isoniazid 300 mg, once daily (with pyridixine 500 mg, once daily) for 9 months; Active tuberculosis should be ruled out before initiating treatment with isoniazid.	Abnormal liver-enzyme levels, peripheral neuropathy.	Risks and benefits of alternative prophylactive regimens should be carefully evaluated on an individual basis.
Streptococcus Pneumoniae	Any, but, response to vaccine is better in persons with >200.	23-valent pneumococcal polysaccharide vaccine; need for revaccination after 5 years has not been established.	Local reaction at site of injection; transient systemic symptoms	
Influenza virus	Any	Inactivated influenza vaccine once years.	Local reaction at site of injection; transient systemic symptoms.	Oseltamivir 75 mg once daily during outbreak if not protected by vaccination.
Hepatitis A virus	Any	Hepatitis a Vaccine	Local reaction at site of injection.	Combined hepatitis A and B vaccine now available.
Hepatitis B virus	Any	Hepatitis B vaccine	Local reaction at site of injection; transient systemic symptoms.	Combined hepatitis A and B vaccine now available.

☆G6PD denotes glucose-6-phospate dehydrogenase. Data are from the CD24 and the U.S. Public Health Services.

**In the following conditions the ARV (Anti retroviral therapy) should not be started if**

1. severe or end stage liver failure
2. severe or end stage kidney failure
3. severe cardiomyopathy or advanced stage of cardiac disease
4. serious clinical and psycho-social conditions

**Conclusions:**

Acute HIV-1 infection, which often presents as an acute febrile illness that is undiagnosed or misdiagnosed, should be considered in the differential diagnosis in any sexually active or otherwise at-risk person presenting with an acute febrile illness. If acute HIV-1 infection is suspected, HIV-1 RNA and HIV-1 ELISA testing should be performed. The use of quantitative HIV-1 RNA testing (or, if unavailable, p24 antigen testing) allows for the diagnosis of acute HIV-1 infection before standard ELISAs detect HIV-1 antibodies.

Once the diagnosis has been established, early treatment with maximally suppressive combination agents should be considered. Adherence to the complicated regimens is essential if early therapy is initiated. Identification of the source of exposure in persons with primary HIV-1 infection may reveal networks of newly infected or highly infectious persons for whom referral and treatment may be beneficial, which in turn may reduce the chance of spread to others.

**References:**

1. Volume 353:1702-1710 Number 16 October 20 2005 NEJM
2. Volume 354:251-260 Number 3 Jan 19 2006 NEJM
3. Guidelines for the use of antiretroviral agent in HIV infected adults and adolescents, DHHS, USA-Feb 2002.