

# HIV / AIDS

## Virology

<b>Lentivirus</b> , class of human retrovirus group (others: oncornavirus and spumavirus). Single stranded RNA genome with envelope	<i>gag</i>	group specific antigen Precursor (p55) to following proteins: Matrix protein (p17), capsid (p24), nucleocapsid (p9)	forms the skeleton of virus
Lentivirus family includes HTLV1 and 2, HIV-1 and HIV-2	<i>pol</i>	polymerase integrase Reverse transcriptase (p64, p53), endonuclease, integrase (p34), protease (p11)	enzymatic functions
<b>Other mammalian lentiviruses:</b> Bovine immunodeficiency virus (BIV), Simian immunodeficiency virus (SIV), Maedi Visna virus (MVV) ⇔ sheep encephalitis /pneumonitis Equine infectious anemia virus (EIAV) Feline immunodeficiency virus (FIV)	<i>env</i>	Envelope Surface glycoprotein (gp120), transmembrane component (gp41), precursor (gp160)	Outer membranes, regulation
	<i>tat</i> , <i>rev</i> , <i>nef</i>	<b>Early regulatory proteins:</b> Enhanced transcription of viral antigens Modulates transport of virion particles Modulates CD4 expression, facilitates replication	
<b>1-Binding of the envelope protein gp 120 to the cellular CD4 molecule:</b> very specific / highly efficient. The affinity of CD4/gp120 > CD4/natural ligand (histocomp MHC2). <b>2-Internalization:</b> fuses w cell membrane. Viral Gp24 <b>3-Reverse transcription:</b> reverse transcriptase makes a cDNA (double stranded DNA proviral intermediate) <b>4-Latent phase</b> 5-Acute viral replication	<i>vif</i> <i>vpu</i> <i>vpx</i> <i>vpr</i>	<b>Late regulatory protein:</b> Modulates infectivity Regulates maturation (HIV-1) Regulates maturation (HIV-2) Facilitates replication	
		<b>Genetic variability explained by the lack of proof reading by the reverse transcriptase (RT).</b> The error prone RT enzyme misspells (incorporates the wrong base) at the rate of 1/10,000 bases.	
<b>History of HIV/AIDS discovery</b> - Jun 81: 5 deaths from <i>Pneumocystis carinii</i> pneumonia among homosexual men in Los Angeles -Dec 81: outbreak of Kaposi's sarcoma in 20 MSM w profound cellular immunodeficiency and Kaposi's sarcoma. 1982: Acquired Immune Deficiency Syndrome ( <b>AIDS</b> ) with high risk: transfusion recipients, hemophiliacs, injection drug users, heterosexuals men and women from Haiti, sexual contacts of infected cases, children of affected women. 1984: HIV-1 (Lymphadenopathy associated virus or LAV discovered by a group from Institute Pasteur, Paris		<b>TEN major Subtypes</b> A: Sub-Saharan Africa G: West & Central Africa C: Heterosex South Africa, Horn of Africa, India, SE Asia B: Pandemic of infection among MSM & IVDU worldwide D: Heterosex Eastern Africa E: Heterosex Asia, Thailand F: Heterosex Central Africa, South America H: Central Africa O: outlier, Central Africa	

## Epidemiology

%Risk of transmission from a single contact with infected partner		Viral load in blood, semen & CD4 count
M ⇒ F	0.1 - 3	Viral load in blood depends on status of the infection
F ⇒ M	0.001 - 1	Semen viral load not related to blood VL or CD4 count.
M ⇒ M	0.8 - 3	Patients with mean CD4 of 338 (range 0-1034)
%Risk of transmission from a relationship with an infected partner		Blood VL 10,000 to 525,000 copies /ml
M ⇒ F	10 - 28	Semen VL 400 to 10 million copies /ml.
F ⇒ M	0 - 8	
M ⇒ M	10	
%Risk of transmission in non sexual setting		
Blood transfusion	60 - 72	
Needle stick, health worker	0.3 - 0.9	
Perinatal transmission	12 - 30	

## Case Definition

CDC disease staging system (1993)	CD4+ T-Cell Cat	Clinical categories		
assesses severity of HIV disease <ul style="list-style-type: none"> <li>by CD4 cell counts</li> <li>by the presence of specific HIV-related conditions</li> </ul>		A Asymptomatic acute primary HIV or PGL (1)	B Symptomatic, not A or C conditions (2)	C AIDS-indicator conditions (3)
The definition of AIDS includes all HIV-infected individuals with CD4 counts of <200 cells/μL (or CD4 percentage <14%) as well as those with certain HIV-related conditions and symptoms.	(1) ≥500/μL (2) 200-499/ μL (3) <200/ μL AIDS indic T-cell count	A1	B1	C1
<b>Category B symptomatic conditions</b> = symptomatic conditions occurring in an HIV-infected adolescent or adult that meet at least 1 of the following criteria: <ul style="list-style-type: none"> <li>attributed to HIV infection or indicate a defect in CMI.</li> <li>considered to have clinical course complicated by HIV infection.</li> </ul> <b>Examples include, but are not limited to, the following:</b> <ul style="list-style-type: none"> <li>Bacillary angiomatosis</li> <li>Oropharyngeal candidiasis (thrush)</li> <li>Vulvovaginal candidiasis, persistent or resistant</li> <li>Pelvic inflammatory disease (PID)</li> <li>Cervical dysplasia (moderate or severe)/cervical carcinoma in situ</li> <li>Hairy leukoplakia, oral</li> <li>Idiopathic thrombocytopenic purpura</li> <li>Constitutional symptoms, fever (&gt;38.5°C) or diarrhea &gt;1 month</li> <li>Peripheral neuropathy</li> <li>Herpes zoster (shingles), involving ≥2 episodes or ≥1 dermatome</li> </ul>	<b>CDC Classification System: Category C AIDS-Indicator Conditions</b> <ul style="list-style-type: none"> <li>Bacterial pneumonia, recurrent (≥2 episodes in 12 months)</li> <li>Candidiasis of the bronchi, trachea, or lungs</li> <li>Candidiasis, esophageal</li> <li>Cervical carcinoma, invasive, confirmed by biopsy</li> <li>Coccidioidomycosis, disseminated or extrapulmonary</li> <li>Cryptococcosis, extrapulmonary</li> <li>Cryptosporidiosis, chronic intestinal (&gt;1-month duration)</li> <li>Cytomegalovirus disease (other than liver, spleen, or nodes)</li> <li>Encephalopathy, HIV-related</li> <li>Herpes simplex: chronic ulcers (&gt;1-month duration), or bronchitis, pneumonitis, or esophagitis</li> <li>Histoplasmosis, disseminated or extrapulmonary</li> <li>Isosporiasis, chronic intestinal (&gt;1-month duration)</li> <li>Kaposi sarcoma</li> <li>Lymphoma, Burkitt, immunoblastic, or primary central nervous system</li> <li><i>Mycobacterium avium</i> complex (MAC) or <i>M kansasii</i>, disseminated or extrapulmonary</li> <li><i>Mycobacterium tuberculosis</i>, pulmonary or extrapulmonary</li> <li><i>Mycobacterium</i>, other species or unidentified species, disseminated or extrapulmonary</li> <li><i>Pneumocystis jiroveci</i> (formerly <i>carinii</i>) pneumonia (PCP)</li> <li>Progressive multifocal leukoencephalopathy (PML)</li> <li><i>Salmonella</i> septicemia, recurrent (nontyphoid)</li> <li>Toxoplasmosis of brain</li> <li>Wasting syndrome due to HIV (involuntary weight loss &gt;10% of baseline body weight) associated with either chronic diarrhea (≥2 loose stools per day ≥1 month) or chronic weakness and documented fever ≥1 month</li> </ul>			
<b>WHO Clinical Staging of HIV/AIDS for Adults and Adolescents</b>				
<b>Primary HIV Infection</b> <ul style="list-style-type: none"> <li>Asymptomatic</li> <li>Acute retroviral syndrome</li> </ul>	<b>Clinical Stage 4</b>			
<b>Clinical Stage 1</b> <ul style="list-style-type: none"> <li>Asymptomatic</li> <li>Persistent generalized lymphadenopathy</li> </ul>	HIV wasting syndrome, as defined by the CDC (see Table 3, above) <ul style="list-style-type: none"> <li><i>Pneumocystis</i> pneumonia</li> <li>Recurrent severe bacterial pneumonia</li> <li>Chronic herpes simplex infection (orolabial, genital, or anorectal site for &gt;1 month or visceral herpes at any site)</li> <li>Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)</li> <li>Extrapulmonary tuberculosis</li> <li>Kaposi sarcoma</li> <li>Cytomegalovirus infection (retinitis or infection of other organs)</li> <li>Central nervous system toxoplasmosis</li> <li>HIV encephalopathy</li> <li>Cryptococcosis, extrapulmonary (including meningitis)</li> <li>Disseminated nontuberculosis <i>Mycobacteria</i> infection</li> <li>Progressive multifocal leukoencephalopathy</li> <li>Candida of the trachea, bronchi, or lungs</li> <li>Chronic cryptosporidiosis (with diarrhea)</li> <li>Chronic isosporiasis</li> <li>Disseminated mycosis (eg, histoplasmosis, coccidioidomycosis, penicilliosis)</li> <li>Recurrent nontyphoidal <i>Salmonella</i> bacteremia</li> <li>Lymphoma (cerebral or B-cell non-Hodgkins)</li> <li>Invasive cervical carcinoma</li> <li>Atypical disseminated leishmaniasis</li> <li>Symptomatic HIV-associated nephropathy</li> <li>Symptomatic HIV-associated cardiomyopathy</li> <li>Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)</li> </ul>			
<b>Clinical Stage 2</b> <ul style="list-style-type: none"> <li>Moderate unexplained weight loss (&lt;10% of body weight)</li> <li>Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis)</li> <li>Herpes zoster, Angular cheilitis, Recurrent oral ulceration</li> <li>Papular pruritic eruptions</li> <li>Seborrheic dermatitis</li> <li>Fungal nail infections</li> </ul>				
<b>Clinical Stage 3</b> <ul style="list-style-type: none"> <li>Unexplained severe weight loss (&gt;10% of body weight)</li> <li>Unexplained chronic diarrhea for &gt;1 month</li> <li>Unexplained persistent fever for &gt;1 month (&gt;37.6°C, intermittent or constant)</li> <li>Persistent oral candidiasis (thrush)</li> <li>Oral hairy leukoplakia</li> <li>Pulmonary tuberculosis (current)</li> <li>Severe presumed bacterial infections (eg, pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)</li> <li>Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis</li> <li>Unexplained anemia (hemoglobin &lt;8 g/dL)</li> <li>Neutropenia (neutrophils &lt;500 cells/μL)</li> <li>Chronic thrombocytopenia (platelets &lt;50,000 cells/μL)</li> </ul>				

## Clinical

**Primary infection:** Incubation 2-6 weeks. 50 to 70% recent infection with acute viral syndrome; ILI: fever, night sweats, arthralgia, myalgia, malaise, headache, nausea, vomiting, diarrhea, and anorexia. Also pharyngitis, rash, weight loss, lymphadenopathy, leukopenia and thrombocytopenia in addition to meningitis, neuropathy and encephalopathy. Syndrome is no different from other viral infections. VL very high, VL ↓ as antibody level ↑

**Chronic infection:** Completely latent infection; rarely persistent generalized lymphadenopathy (PGL); trend in CD4+ count over period of time is best indicator of HIV infection progress.

<p><b>HIV direct effects:</b> direct consequences of the multiplication of HIV AIDS dementia, aseptic meningitis, distal sensory neuropathy autonomic neuropathy diarrhea</p>	<p><b>Opportunistic infections</b> <i>P. carinii</i> pneumonia Tuberculosis <i>Mycobacterium avium</i> infection <i>Cryptococcus neoformans</i> meningitis Toxoplasma encephalitis CMV chorioretinitis</p>	<p>Oral candidiasis (thrush) Persistent Herpes simplex infections Shingles Histoplasmosis, coccidioidomycosis (endemic areas) Tuberculosis Severe diarrhea</p>
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<p><b>Cancer</b> -Kaposi's sarcoma: appears sooner, more common among homosexuals Non-Hodgkin lymphoma B-cell lymphoma Anal and cervical also associated with HIV infection</p>	<p><b>Long Term Asymptomatic individuals</b> Common period from infection to AIDS onset = 7 to 11 years without Tx Some HIV-1 infected are symptoms free &gt;12 years after infection. CD4+ count shows no decrease. (1983 SFO MSM cohort -539- 8% symptom free &amp; CD4+ count ≥500 /mm<sup>3</sup> for &gt; 12 years.</p>
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Progress	Duration	Phase	Viral load	Antigen/Antibodies					CD4
				P24 Ag	P24 Ag WB	IgM EIA	IgG EIA	IgG WB	
	0-2 wks	Incubation							
	0-1 wks	Acute HIV syndrome	↑	0 – 2 wks		5days	11days		1200
	2-3 wks		200,000/mL		3-4 wks	Peak15 days		3 wks	
		Resolution PHI				3mos			
	Years	Latent							
		AIDS							400
		Opportunistic infections							
	10-12 yrs	Death							

## Lab Diagnostic

### Antibody testing

**1-Sensitive screening test** as ELISA) or rapid assay.

- False positive may be due to passive transfer of antibody at birth (end at 15 months) or cross reactions with other viral antigens
- False negative should be kept at minimum by design: The most common type of false negative would occur at the beginning of the infection. Newer tests have included recombinantly produced viral peptides to enhance sensitivity.

### 2-Confirmed by Western blot

**Early window period:** HIV antibody is detectable in >95% of patients within 6 months of infection. Although a negative antibody test usually means a person is not infected, antibody tests cannot rule out infection that occurred <6 months before the test.

**Some variants** (variant 0 isolated in Cameroon) may be missed by some of the currently used tests (1996). Better testing materials are constantly being developed to avoid such false negatives.

**Rapid Test:** The sensitivity and specificity of rapid assays are comparable to those of EIAs.

**-Neg:** In low prevalence areas, negative predictive value of a single rapid test is high. A negative rapid test does not require further testing,

**-Pos:** In low prevalence areas, positive predictive value of a test is low. Reactive rapid test must be confirmed by a supplemental test.

**HIV 2:** HIV -1 and HIV-2 share 60% of nucleotide sequence for *gag* and *pol* glycoproteins and 40% for *env*. Screening tests for HIV-1 may sometimes be unreliable for HIV-2. There are some specific screening and confirmatory tests for HIV-2. These should be used whenever HIV-2 is suspected.

When to screen for HIV-2:

**1-NOT systematically:** The prevalence of HIV-2 in the United States is extremely low, and CDC does not recommend routine testing for HIV-2 in settings other than blood centers, unless demographic or behavioral information suggests that HIV-2 infection might be present.

**2-All blood donations:** Since 1992, blood donations in the USA are screened with a FDA licensed test for both HIV-1 and HIV-2.

**3-Those at high risk of HIV-2:** Those at risk for HIV-2 infection include persons from a country in which HIV-2 is endemic or the sex partners of such persons. (As of July 1992, HIV-2 was endemic in parts of West Africa and an increased prevalence of HIV-2 had been reported in Angola, France, Mozambique, and Portugal). Additionally, testing for HIV-2 should be conducted when there is clinical evidence or suspicion of HIV disease in the absence of a positive test for antibodies to HIV-1.

**4. HIV-1 positive EIA with negative W blot:** Use a HIV-2 EIA and if positive confirm with an HIV-2 W blot.

### Criteria for Positive Interpretation of Western Blot

Organization	Criteria
Assoc State & Territorial Public Health Laboratory Directors/CDC	Any two of p24 or gp41 or gp120/gp160*
FDA-Licensed Du Pont test	p24 and p31 and gp41 or gp120/gp160
American Red Cross	≥3 bands - 1 from each gene-product group: GAG and POL and ENV
Consortium for Retrovirus Serology Standardization	≥2 bands: p24 or p31, plus gp41 or gp120/gp160

**Viral antigenemia:** HIV in peripheral blood: 1-elec microscopy, 2-p24 antigenemia, 3-viral culture: expensive & cumbersome

HIV in asymptomatic = 1 in 50,000 peripheral blood mononuclear cell (PBMC); symptomatic AIDS = 1 in 40 PBMC harbors HIV

**PCR** more sensitive than viral culture or p24 antigen detection. False positive are rare, they are due to contamination of negative sample, reagent contamination, carry over from a positive sample. False negatives result from compromised analytic techniques.

**PCR quantitation of proviral DNA** in PBMC

HIV-1 RNA in serum, confirmation of HIV when doubtful results, in newborns, seronegative individuals

**CD4+ count** used as a staging tool, indicating progression towards immune suppression; Use same laboratory and, obtain at same time each day. When unexpected or discrepant results or major treatment decisions: repeat CD4+ measurement after >1 week.

## Diagnostic Evaluation

### Initial Evaluation

1. Complete medical history with emphasis on opportunistic infections including constitutional symptoms, candidiasis, pneumonia, gastrointestinal symptoms, dates and results of previous PPDs, treatment of TB, STDs, results and dates of previous Pap smears.
2. Determine HIV risk behavior and access ongoing high-risk behavior
3. Patient exam for candidiasis, fundoscopic exam, lymphadenopathy, lungs, hepatosplenomegaly, skin disease, STDs, gynecologic exam.
4. Laboratory tests
 

CBC	Baseline chest x-ray
CD4 count	CMV serology (if low risk)
Chemistry profile	STD screen; RPR or VDRL, +GC and chlamydia screen (women)
Toxoplasma serology (IgG)	Varicella screen
Chest x-ray*	Hepatitis screen: anti-HBc (? HBV vaccine); HBsAg; anti-HCV
PPD (if not done)	Pap smear (if none in past year)
5. PCP prophylaxis if reliable history of PCP or thrush
6. Immunization: Review immunization status and update according to Guidelines.

Test	Indication
<b>Viral loads</b>	[HIV RNA] concentration in blood. Baseline, at initiation of Tx, 1 month, q 3-4 months, and anytime something happens
<ol style="list-style-type: none"> <li>1. Measure magnitude of infection</li> <li>2. Measures progression to disease: a high viral load, even at the beginning of infection indicates fast progress</li> <li>3. Evaluates response to treatment</li> </ol> Threshold of detection of viral load depends on the tests: 200, 1,000... Viral load drops expressed as logs. VL 1,000,000 drops to 1,000: 1,000 = 3 logs, (log (10))=1. Drop proportional to number of active medications: 3 log drop ⇔ 4 medications	SFO MSM ⇔ predictive value Viral load% AIDS in 10 years <10,000            10% >110,000           75%
CD4 measure the distance from infection to death, viral load measure how fast disease is progressing (speed)	
<b>HIV serology</b>	Confirmation of diagnosis only
Need confirmed test with standard serologic method. Repeat test if no confirmed test available or denial of commonly accepted risks. No need to repeat after diagnosis firmly established.	
<b>CBC</b>	Initial evaluation and 6 mo
Repeat at 6-mo intervals: more frequently as indicated for low values (anemia, neutropenia or thrombocytopenia) and with marrow-suppressing drugs	
<b>CD4 count &amp; %</b>	Initial evaluation and every 6 mo
<ul style="list-style-type: none"> <li>• &gt;500/mm<sup>3</sup>: Repeat CD4 count q 6 mo</li> <li>• 200-500/mm<sup>3</sup>: Repeat CD4 count q 6 mo (more frequently if decline is rapid)</li> <li>• &lt;200/mm<sup>3</sup>: PCP prophylaxis</li> <li>• &lt;100/mm<sup>3</sup> &amp; Toxoplasma IgG+: Toxoplasma <i>prophylaxis</i></li> <li>• (if TMP-SMX for PCP contraindicated)</li> <li>• &lt;75/mm<sup>3</sup>: Consider <i>M. avium</i> prophylaxis</li> </ul> Indications for CD4 counts when <50/mm <sup>3</sup> are arbitrary Repeat test with "outlier results" based on prior counts especially when decisions about prophylaxis, diagnostic tests, or treatment are based on CD4 count or if patient anxiety demands it.	
<b>VDRL or RPR</b>	Initial evaluation and annually
Repeat annually if sexually active False-positive and -negative results are reported Patients with positive results and positive FTA should have Lumbar puncture	
<b>Chemistry panel</b>	Initial evaluation and prn
Repeat annually; more frequently as indicated for abnormal results and with hepato-toxic or nephro-toxic drugs	
<b>Hepatitis serology</b>	Initial evaluation
Screen candidates for HBV vaccine with anti-HBc Patients with abnormal liver function tests: test anti-HCV and HBsAg	
<b>Toxoplasmosis serology</b>	Initial evaluation and if neg initially retest when CD4 ≤100
Initial IgG negative: counsel regarding prevention of exposure Repeat in seronegative patients when they become candidates for prophylaxis (CD4 ≤100 and pos toxoplasma serology)	
<b>CMV serology</b>	Low-risk patients
Initial IgG CMV negative: Counsel re prevention of acquisition and use of leukocyte filtration with transfusions.	
<b>PPD</b>	Initial evaluation and annually for non significant tests
Repeat for non significant test results. Anergy screen in nonreactors is optional due to lack of standardization of reagents and inconsistent results If done use two of three test antigens: <i>C. albicans</i> , tetanus toxoid, and mumps.	
<b>Pap smear</b>	Initial evaluation, 6 mo after and then annually
Repeat if inadequate endocervical component. Results showing atypia or CIN 1-3: refer to gynecologist. Some advocate Pap smear q 6 months for those with CD4 <500	
<b>Chest x-ray</b>	Initial evaluation and prn
Repeat only for clinical evaluation. Some question the need for a baseline x ray if asymptomatic patient with neg PPD	
<b>G-6-PD level</b>	Initial evaluation and evaluation of unexplained hemolytic anemia
Necessary since patients will be considered for antioxidant drugs (especially dapsone or primaquine). Measure methemoglobin during suspected hemolysis	

## Opportunistic Infection Prevention

Disease	Indications	Preferred Regimen
<b>Tuberculosis (high priority)</b>	<ul style="list-style-type: none"> <li>• PPD <math>\geq</math> 5 mm induration)</li> <li>• Prior positive PPD without INH prophylaxis</li> <li>• High-risk exposure</li> </ul>	INH 300 mg/d + pyridoxine 50 mg/d for 12 mos
Efficacy established, Alternative is rifampin 600 mg/d x 12 mo		
<b><i>P. carinii</i> pneumonia (high priority)</b>	<ul style="list-style-type: none"> <li>• Prior PCP</li> <li>• CD4 &lt; 200</li> <li>• Thrush or Fever of unknown origin <math>\geq</math> 100 °F for <math>\geq</math> 2 weeks</li> </ul>	Trimethoprim-Sulfamethoxazole (TMP-SMX) 1 DS/d
Efficacy established: cost effective, reduced morbidity and mortality. Alternatives: <ul style="list-style-type: none"> <li>• TMP-SMX 1 SS (single strength) daily</li> <li>• TMP-SMX 1 DS 3 days / wk</li> <li>• Dapsone 50mg/day + Pyrimethamine 75mg/week + Leucovorin 25 mg/week</li> <li>• Aerosolized pentamidine</li> </ul>		
<b>Toxoplasmosis (high priority)</b>	CD4 $\leq$ 100 with positive serology (IgG)	TMP-SMX 1 DS/d
Efficacy established. Main issue is use of alternative regimens in patients with TMP-SMX intolerance: <ul style="list-style-type: none"> <li>• Dapsone 50 mg/day + pyrimethamine 50 mg/wk + leucovorin 25 mg/wk</li> <li>• Dapsone 200 mg/wk + pyrimethamine 75 mg/wk + leucovorin 25 mg/wk</li> </ul>		
<b><i>M. avium</i> (moderate priority)</b>	CD4 $\leq$ 75	Rifabutin 300 mg/d
Efficacy established. Alternative regimen: <ul style="list-style-type: none"> <li>• Clarithromycin 500 mg bid</li> <li>• Azithromycin 1250 mg 1 x/wk</li> </ul> Clarithromycin is superior to rifabutin for MAC prophylaxis and FDA approved Azithromycin appears as effective as clarithromycin A disadvantage of macrolides is possible resistance to clarithromycin which is the favored agent for treatment of established infection. A disadvantage of rifabutin is multiple drug interactions		
<b>CMV</b>	CD4 $\leq$ 50	Oral ganciclovir 1000 mg po tid
(no formal recommendation) Efficacy shown in the Syntex study, but not in CPCRA 023. Concerns are cost, promotion of ganciclovir resistance, and preliminary state of data. Many authorities feel that indications for CMV prophylaxis will be redefined by use of PCR to detect CMV in blood or quantitative PCR CMV: If seronegative—non-emergent blood transfusions: Give only CMV antibody-negative or leukocyte-reduced cellular blood products.		
<b>Deep fungal infection</b>	CD4 $\leq$ 100	Fluconazole 200 mg/d
(not recommended for most patients) Efficacy established for prevention of cryptococcosis, and <i>Candida</i> esophagitis and thrush. Concerns are cost, lack of evidence for prolongation of survival and promotion of infection with azole-resistant <i>Candida</i> spp.		

## Vaccinations

Vaccine	Indication	Regimen
<b>Routine</b>		
Pneumococcal vaccine	All HIV patients	0.5 mL IM
Risk of <i>S. pneumoniae</i> x 100-fold, but vaccine efficacy in HIV-infected patients is not established. Antigenic response is best when CD4 count is >350		
Influenza vaccine	All HIV patients in Oct-Dec	0.5 mL IM
Risk of influenza not clearly x, but prevention avoid expensive and complicated diagnostic evaluation of flu-like complaints.		
Hepatitis B vaccine	See comments	3 IM doses at 0, 1, and 6 mo. Recombivax: 10 ~19 Energix: 20 ug
Indications: Seronegative IDU, sexually active gay men, heterosexual men and women with STD or >1 sex partner in past 6 mo and household or sex contacts of HBsAg carriers Screening test is anti-HBc; Risk of becoming HBsAg carriers $\uparrow$ with HIV infection; Measure antibody response in HIV patients at 1- 6 months after 3rd dose: non-responders should receive 1-3 boosters		
<b>Travel-associated</b>		
Oral polio	Contra indicated; eIPV preferred	
Inactivated polio (eIPV)	Travel to developing countries for those without prior immunization	0.5 mL subcutaneously
Preferred for HIV-infected persons and close contacts;		
Yellow fever	Contra indicated	
Live vaccine. With travel to endemic area advise patient of risk, instruct in control of mosquito exposure and provide vaccination waiver letter		
Japanese B. encephalitis	Travel >1 mo to epidemic area	1 mL subcutaneously x 3 at days 0, 7 and 30
Expensive and side effects (not unique to HIV infected persons)		
Typhoid (ViCSP)	Travel to risk area	0.5 mL intramuscularly x 1.
The live attenuated Ty21a vaccine (Vivotif) is contraindicated. ViCSP is the new Vi capsular effective than the parenteral which is no more vaccine, but causes fewer side effects and requires only one dose		
Typhoid inactivated vaccine	Travel to risk area	0.25 mL x 2 separated by 1 month
Hepatitis A	Travel, Gay men, Injection drug users	1 mL mo. x 12-14 days prior
Havrix was FDA approved in 1995 and may be intramuscularly used in place of immune globulin. Serologic tests show 30% of adults are protected by prior infection		

## Treatment

**1-The envelope protein, gp120**, is essential for viral entry into host cells, which makes it a candidate for vaccine studies. There are no drugs available that prevent the HIV virus from entering and infecting host cells.

**2a-Nucleoside Reverse Transcriptase Inhibitors**, nucleoside analogues or (**NRTIs**, **NUKES**). First group of drugs used for AIDS Tx. Nucleoside agents compete with naturally occurring nucleosides for incorporation into the viral DNA, ⇒ adverse reactions (eg, anemia, neutropenia).

**2b-Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

**3-Protease inhibitors**. HIV protease = viral enzyme required for assembling new virus particles. When used in combination with 2 nucleoside analogues, protease inhibitor therapy can reduce the viral load (the amount of virus circulating in plasma) 100- to 1000-fold, and potentially suppress viral replication

**2008 Recommendations of the International AIDS Society-USA Panel; JAMA. 2008; 300(5):555-570.**

**When to start** (Primary HIV infection: no definitive evidence to supports routine initiation of antiretroviral therapy)

--all patients with symptomatic established HIV disease after appropriate counseling.

--asymptomatic individuals, before CD4 < 350/μL decisions based on comorbidities, risk of disease progression, patient willingness, adherence

--rapid decline in CD4: >100/μL per year

--plasma HIV-1 RNA >100 000 copies/mL

Risk factors for cardiovascular disease, hypertension, hyperlipidemia, diabetes, tobacco use, to be aggressively managed (risk ↑ with hi VL)

no upper CD4 cell limit for starting therapy when 1 or more of these considerations are present

**Initial Regimen:** factors to consider

drug susceptibility, pill burden, frequency of dosing, anticipated tolerability, comorbid conditions, and short- and long-term adverse event profiles

NRTI	NNRTI	Protease
Nucleoside analog which inhibits reverse transcriptase	Non nucleoside analog which inhibits reverse transcriptase	
<b>Zidovudine, AZT, ZDV, Retrovir</b> 300mg bid, meals OK Side Effect: Anemia, neutropenia, NV, headache, fatigue,, myopathy, hepatitis No proven teratogenicity in pregnant women Resistance develops rapidly	<b>Nevirapine, Viramune</b> 200mg bid, meals OK Side Effect: rash, hepatic necrosis	<b>Saquinavir, Invirase</b> 1,200mg tid Side Effect: NVD, hyperglycemia, ↑transaminase, bleeding in hemoφ
<b>Didanosine, DDI, Videx</b> 200mg bid, away from meals Side Effect: Pancreatitis, painful peripheral neuropathy, GI, hepatitis. Resistance some	<b>Delavirdine, Rescriptor</b> 400mg tid, meals OK Side Effect: rash, ↑transaminases	<b>Ritonavir, Norvir</b> Potent antiretroviral (↓log2/3) >1year Side Effect: High; NVD, hep, asthenia, rash, hyperglycemia, hemolytic anemia, bleeding in hemoφ
<b>Zalcitabine, DDC, Hivid</b> 0.75mg tid, meals OK Side Effect: Pancreatitis Painful peripheral neuropathy, rash, stomatitis Resistance some	<b>Efavirenz, Sustiva</b> 600mg qd pm Side Effect: rash, ↑transaminases; not recommended for women in the first trimester of pregnancy or contemplating pregnancy	<b>Indinavir, Crixivan</b> Potent, ↓log 2/3; 800mg tid, meals away, complicated dosing Side Effect: nephrolithiasis, hep, rash, hyperglycemia, alopecia, hemolytic anemia, bleeding in hemoφ
<b>Lamivudine, 3TC</b> 150mg bid, meals OK Side Effect: Better tolerance than others With AZT = <b>Combivir</b> With AZT + Abacavir = <b>Trizivir</b>		<b>Nelfinavir, Viracept</b> Potent anti-HIV effect. Side Effect: Well tolerated; D
<b>Stavudine, d4T, Zerit</b> 40mg bid, meals OK Side Effect: Pancreatitis, peripheral neuropathy		<b>Lopinavir, Kaletra (lopinavir + ritonavir)</b> 400/100mg bid, meals OK Side Effect: NVD, fatigue, pancreatitis, hep, bleeding in hemoφ
<b>Abacavir, Ziagen</b> 300mg bid, meals OK, alcohol ↑level Side Effect: fever, rash, vomit, respiratory		<b>Amprenavir, Agenerase</b> 1,400mg bid, meals OK no fat, CI: renal or hep failures Side Effect: NVD, hyperglycemia,
<b>Tenofovir, Viread</b> 300mg qd, Side Effect: Asthenia, NVD, hepatitis		

### Regimen of choice

**2nRTIs + Efavirenz or 2nRTIs + Ritonavir/Lopinavir** : Simplicity of therapy, pill number, tolerability, drug interactions, primary drug resistance, and comorbid conditions are likely to influence the choice between these 2 recommended options.

**Efavirenz + Ritonavir/Lopinavir**

Treatment for patients with transmitted drug resistance should be guided by resistance test results

### Monitoring Treatment Response

Effective therapy should generally result in at least a 10-fold (1.0 log<sub>10</sub>) decrease in HIV-1 RNA copies/mL in the first month and suppression to less than 50 copies/mL by 24 weeks, depending on pretreatment viral load.<sup>1</sup> Once HIV-1 RNA suppression is confirmed, it should be assessed at regular intervals (eg, every 3 or 4 months).<sup>1</sup> Isolated episodes of low-level viremia ("blips") are not predictive of subsequent virologic failure, but consistent elevations to more than 50 copies/mL meet a strict definition of virologic failure.

The goal of antiretroviral therapy is to **reduce and maintain a plasma HIV-1 RNA level of less than 50 copies/mL**, regardless of previous treatment experience. Plasma HIV-1 RNA levels should be monitored frequently when treatment is initiated or changed for virologic failure (eg, at 2, 4, 8, and every 4 weeks thereafter) until it reaches levels below the assay detection limits, and regularly thereafter (eg, 3-4 times per year). Once the viral load is suppressed for an extended period and CD4 cell counts are stable at 350/μL or more, twice-yearly CD4 cell counts are reasonable.