Initiation of Antiretroviral Therapy

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Human immunodeficiency virus type I (HIV-I) causes the acquired immunodeficiency syndrome (AIDS), a chronic illness characterized by progressive immune and neurologic dysfunction. HIV- I also causes the acute viral syndrome with variable manifestations, most frequently fever, lymphadenopathy, pharyngitis and rash. Recently, the availability of new antiretroviral regimens have dramatically changed the treatment strategies for persons infected with HIV-I. With potent protease inhibitors in combination therapy regimens, lower morbidity and longer survival have been achieved. However, the questions of when to start therapy and what regimens to use have not been well understood. Therefore, this article reviews guidelines for the use of antiretroviral agents in HIV-infected adults.

High level of viral replication can be demonstrated at the time of initial infection and throughout the subsequent course. Recent data demonstrate that estimated average total HIV-I production is 10 x 10^9 virions per day and the minimum duration of the HIV- I life cycle in vivo is 1.2 days. Productively infected cells are estimated to have, an average, a life span of 2.2 days. (half-life = 1.6 days). These results also suggest that the average HIV-I generation time, defined as the time from release of a virion until it infects another cell and causes the release of a new generation of viral particles, is 2.6 days. [1] These findings with regard to viral dynamics provide not only a kinetic picture of HIV-I pathogenesis, but also theoretical principles to guide the development of treatment strategies. Based on these viral dynamics, the goal of treatment should be a dramatic decrease in the number of actively replicating viruses in order to slow the assault on the immune system and to decrease the emergence of drug-resistant viral variants. In deciding when to begin antiretroviral therapy, two distinct clinical situations deserve consideration : acute HIV infection and established HIV infection.

Acute HIV infection is generally defined as the the time between initial infection with HIV and the development of an HIV-specific antibody response. The clinical presentation during this stage of disease ranges from asymptomatic seroconversion to a severe symptomatic illness resembling infectious mononucleosis that can result in hospitalization. However, the diagnosis of acute HIV infection should be

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based on strong clinical suspicion and the presence of either HIV p 24 antigen or HIV RNA in the blood. It has also been estimated that at least 50% and as many as 90% of patients acutely infected with HIV will experience some symptoms of the acute retroviral syndrome (Table 1) and can thus be identified as candidates for early therapy. [2 5] Initiation of therapy during acute HIV infection may have a profound impact on altering the natural history of the disease. First, aggressive treatment may dramatically lower the tremendous viremia associated with primary infection [6] and ultimately result in a lower set point of viral replication. (The set point is the level at which plasma viremia stabilizes after initial infection; it may help predict the rapidity of progression.) [7] Second, instituting antiretroviral therapy during primary infection should lower the likelihood of the emergence of divergent viral quasispecies, including viruses resistant to current antiretrovirals. If the viral set point can be effectively lowered and viral load driven below limits of detection in plasma, many feel that this chance of resistance to antiretrovirals may be significantly reduced or prevented altogether. Third, treatment during primary infection may help preserve immune function. HIV-specific defenses are activated during primary infection in an attempt by the immune system to overcome viral infection. It has been hypothesized that, during this critical period, rapidly prolife rating cells of the immune system become targets of viral infection and may be removed from the immunologic repertoire. Thus, aggressive antiretroviral therapy accompanied by a dramatic decline in viral load may play a critical role in preserving the immune system.

From all the clinical studies, many experts would recommend antiretroviral therapy for all patients who demonstrate laboratory evidence of acute HIV infection. Such evidence includes detectable HIV RNA in plasma using sensitive PCR or bDNA assays together with a negative or indeterminate HIV antibody test. While measurement of plasma HIV RNA is the preferable method of diagnosis, a test for p24 antigen may be useful when RNA testing is not readily available. It should be noted, however, that a negative p24 antigen test does not rule out acute infection. When suspicion for acute infection is high, sush as in a patient with a report of recent risk behavior in association with symptoms and signs listed in table 1, a test for HIV RNA should be performed. As noted earlier, individuals may or may not have symptoms of the acute retroviral syndrome. Viremia occurs acutely after infection prior to the detection of a specific immune response; an indeterminate antibody test may occur when an individual is in the process of seroconversion. Apart from patients with acute HIV infection, many experts would also consider therapy for patients in whom seroconversion has been documented to have occurred within the previous six months. Once the physician and patient have made the decision to use antiretroviral therapy for acute HIV infection, treatment should be implemented with the goal of suppressing plasma HIV RNA levels to below detectable levels. The weight of current experience suggests that the therapeutic regimen for acute HIV infection should include a combination of two nucleoside reverse transcriptase inhibitors and one potent protease inhibitor. Although most experience to date with protease inhibitors in the setting of acute HIV infection has been with ritonavir, indinavir or nelfinavir, [8-11] there are insufficient data to make firm conclusions regarding specific drug recommendations. Potential combinations

of agents available are much the same as those used in established infection, listed in table 2. It is recognized that these aggressive regimens may be associated with several disadvantages, including drug toxicity, large pill burden, cost of drugs, and the possibility of developing drug resistance that may limit future options; the latter is likely if virus replication is not adequately suppressed or if the patient has been infected with a viral strain is already resistant to one or more agents. Once therapy is initiated many experts would continue to treat the patient with antiretroviral agents indefinitely because viremia has been documented to reappear or increase after discontinuation of therapy. However, some experts would treat for one year then reevaluate the patient with CD_4 T cell determinations and quantitative HIV RNA measurement. The optimal duration and composition of therapy are unknown and ongoing clinical trials are expected to provide data relevant to these issues.

Patients with established HIV infection are considered in two arbitrarily defined clinical categories: 1. asymptomatic infection or 2. symptomatic disease (wasting, thrush or unexplained fever for ≥ 2 weeks) including AIDS, defined according to the 1993 CDC classification system. All patients in the second category should be offered antiretroviral therapy. Considerations for initiating antiretroviral therapy in the first category of patients are complex. However, before initiating therapy in any patient, the following evaluation should be performed.

- Complete history and physical examination
- Complete blood count, chemistry profile
- CD4 T lymphocyte count
- Plasma HIV RNA measurement

Additional evaluation should include routine tests pertinent to the prevention of opportunistic infections, if not already performed (VDRL, tuberculin skin test, toxoplasma IgG serology, and gynecologic examination with pap smear), and other tests as clinically indicated (e.g. CXR, hepatitis C virus serology, ophthalmologic examination). Hepatitis B virus serology is indicated in a patient who is a candidate for the hepatitis B vaccine or has abnormal liver function tests.

The decision to begin therapy in the asymptomatic patient is complex and must be made in the setting of careful patient counselling and education. The factors that must be considered in this decision are; 1. the willingness of the individual to begin therapy; 2. the degree of existing immunodeficiency as determined by the CD_4 T cell count; 3. the risk of disease progression as determined by the level of plasma HIV RNA ; 4. the potential benefits and risks of initiating therapy in asymptomatic individuals as shown in table 3 ; and 5. the likelihood, after counselling and education, of adherence to the prescribed treatment regimen. To achieve the level of adherence necessary for effective therapy, providers are encouraged to utilize strategies for assessing and assisting adherence that have been developed in the context of chronic treatment for other serious diseases ; in this regard, intensive patient education regarding the critical need for adherence should be provided, specific goals of therapy should be established and mutually agreed upon and a long – term treatment plan should be developed with the patient. Intensive follow up should take place to assess adherence to treatment and to continue patient counselling for the prevention of sexual and drug injection – related transmission.

Once the patient and physician have decided to initiate antiretroviral therapy, treatment should be aggressive with the goal of maximal suppression of plasma viral load to undetectable levels. The recommendations regarding when to initiate therapy and what regimens to use are shown in table 2 and 4 . Depending on the weight of experience, the generally regimen to accomplish this is 2 nucleoside analogues (NRTIS) and one potent protease inhibitor (PI) . Alternative regimens have been employed; these include ritonavir and saquinavir (with one or two nucleoside analogues) or substituting nevirapine for the protease inhibitor. Ritonavir and saquinavir dual protease inhibitor therapy (without an NRTI) appears to be potent in suppressing viremia below detectable levels, and has convenient BID dosing; however, the safety of this combination has not been fully established according to FDA guidelines. When initiating antiretroviral therapy, all drugs should be started simultaneously at full dose with the following three exceptions: dose escalation regimens are recommended for ritonavir, nevirapine, and in some cases, ritonavir plus saquinavir. Dosing recommendation and adverse effects of NRTIS, NNRTIS and protease inhibitors are summarized in table 5. Toxicity assessment is an ongoing process assessment at least twice during the first month of therapy and every 3 months thereafter is a reasonable management approach.

All patients diagnosed with advanced HIV disease, which is defined as any condition meeting the 1993 CDC definition of AIDS should be treated with antiretroviral agents regardless of plasma viral levels. All patients with symptomatic HIV infection without AIDS, defined as the presence of thrush or unexplained fever, should also be treated. When the patient is acutely ill with an opportunistic infection or other complication of HIV infection, the clinician should consider clinical issues such as drug toxicity, ability to adhere to treatment regimens, drug interactions and laboratory abnormalities when determining the timing of initiation of antiretroviral therapy. Once therapy is initiated, a maximally suppressive regimen, such as 2NRTIS and a protease inhibitor, should be used, as indicated in table 2. Advanced stage patients being maintained on an antiretroviral regimen should not have the therapy discontinued during an acute opportunistic infection or malignancy, unless there are concerns regarding drug toxicity, in tolerance, or drug interactions. Table 6 summarizes the drug interactions between protease inhibitors and other drugs. There are multiple reasons for temporary discontinuation of antiretroviral therapy, including intolerable side effects, drug interactions, first trimester of pregnancy when the patient so elects, and unavailability of drug. There are no studies and no reliable estimate of the number of days, weeks or months that constitute a clinically important interruption of one or more components of a therapeutic regimen that would increase the likelihood of drug resistance. If there is a need to discontinue any antiretroviral medication for an extended time, Clinicians and patients should be advised of the theoretical advantage of stopping all antiretroviral agents simultaneously, rather than continuing one or two agents, to minimize the emergence of resistant viral strains.

In Summary, with the advent of viral load testing in conjunction with CD_4 cell monitoring, and with the emergence of more potent therapies that dramatically slow viral replication, principles guiding the initiation at therapy have changed. Many experts recommend initiating a three – drug

regimen consisting of two nucleoside reverse transcriptase inhibitors plus either a protease inhibitor as discussed before. In general, two - drug regimens are no longer recommended because of higher rates of breakthrough viral replication when two drugs are used instead of three. In special circumstances, sometimes two drugs are used; AZT/3TC or d4T/3TC. Of note, monotherapy is no longer recommend with any antiretroviral agents as initial treatment. If the patients are not ready to commit such regimens, it may be better to withhold therapy until they are. Some would advocate that it is better to wait until a patient is ready to adhere to a potent three drug regimen than to begin piecemeal programs of one or two drugs. Decision concerning when to initiate therapy and with what drugs are obviously complex and require careful thought.

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Table 1 Acute retroviral syndrome : associated signs and symptoms (expected frequency)

- Fever (96 %)
- Lymphadenopathy (74 %)
- Pharyngitis (70 %)
- Rash (70 %)
  - Erythematous maculopapular with lesions on face and trunk and sometimes extremities including palms and soles
  - Mucocutaneous ulceration involving mouth, esophagus or genitals
- Myalgia or arthralgia (54 %)
- Diarrhea (32 %)
- Headache (32 %)
- Nausea and vomiting (27 %)
- Hepatosplenomegaly (14 %)
- Thrush (12 %)
- Weight loss
- Neurologic symptoms (12 %)
  - Meningoencephalitis or aseptic meningitis
  - Peripheral neuropathy or radiculopathy
  - Facial palsy
  - Guillain-Barre syndrome
  - Brachial neuritis
  - Cognitive impairment or psychosis

Table 2 Recommended antiretroviral agents for treatment of established HIV infection

Preferred : strong evidence of clinical benefit and/or sustained suppression of plasma viral load [8, 12, 13]

One choice each from column A and column B.*Drugs are listed in random, not priority, order :

Column A	Column B
Indinavir	ZDV + ddI
Nelfinavir	d4T + ddI
Ritonavir	ZDV + ddC
Ritonavir †	ZDV + 3TC ‡
Saquinavir	4dT + 3TC ‡

Alternative : less likely to provide sustained virus suppression; [14]

1NNRTI (nelfinavir) †+ 2NRTIs (column B, above)

Saquinavir (hard gel capsule) + 2NRTIs (column B, above)

Not generally recommended : strong evidence of clinical benefit but initial virus suppression is not sustained in most patients[15, 16]

2NRTIs (column B, above)

Not recommended § : evidence against use, virologically undesirable, or overlapping toxicities

All monotherapies

d4T + ZDV

ddC + ddI ||

ddC + d4T||

ddC + 3TC

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* The current hard gel capsule formulation of saquinaviris not recommended as first line therapy due to poor bioavailability. New formulations developed to increase the bioavailability of saquinavir are currently under study. When using saquinavir+ritonavir, one or two NRTIs should also be used. [17, 18]

† The only combination of 2NRTIs + 1NNRTI that has been shown to suppress viremia to undetectable levels in the majority of patients is ZDV + ddI + Nevirapine. This combination was studied in antiretroviral naive individuals. [14]

‡ High level resistance to 3TC develops within 2–4 weeks in partially suppressive regimens; optimal use is in 3 drug antiretroviral combinations that reduce viral load to <500 copies/ml.

§ ZDV monotherapy may be considered for prophylactic use in pregnant women with low viral load and high CD_4+ T cell counts to prevent perinatal transmission.

|| This combination of NRTIs is not recommended based on lack of clinical data using the combination and/or overlapping toxicities.

Table 3 Risks and benefits of early initiation of antiretroviral therapy in the asymptomatic HIV – infected patient

Potential benefits

- Control of viral replication and mutation, reduction of viral burden
- Prevention of progressive immunodeficiency; potential maintenance or reconstitution of a normal immune system
- Delayed progression to AIDS and prolongation of life
- Decreased risk of selection of resistant virus
- Decreased risk of drug toxicity

Potential risks

- Reduction in quality of life from adverse drug effects and inconvenience of current maximally suppressive regimens
- Earlier development of drug resistance
- Limitation in future choices of antiretroviral agents due to development of resistance
- Unknown long term toxicity of antiretroviral drugs
- Unknown duration of effectiveness of current antiretroviral therapies

Table 4 Indications for the initiation of antiretroviral therapy in the chronically HIV-infected patient

Clinical Category	CD4+ T cell count and HIV RNA	Recommendation
Symptomatic (AIDS, thrush, unexplained fever)	Any value	Treat
Asymptomatic	CD4+ T Cell < 500/mm3 or HIV RNA > 10,000 (bDNA) or > 20,000 (RT-PCR)	Treatment should be offered. Strength of recommendation is based on prognosis for disease-free survival as shown in Table 2 and willingness of the patient to accept therapy.*
	CD4+ T cell > 500/mm3 and HIV RNA < 10,000 (bDNA) or < 20,000 (RT-PCR)	Many experts would delay therapy and observe; however, some experts would treat.

* Some experts would observe patients with CD4+ T cell count between 350 – 500 /mm^3 and HIV RNA levels <10,000 (bDNA) or <20,000 (RT-PCR).

Table 5 Dosing recommendation and adverse effects of NRTIS, NNRTIS and protease inhibitors

Generic name	Trade name	Dosing recommendation	Adverse effects
Nucleoside reverse transcriptase inhibitors (NRTIS)			
Zidovudine (AZT)	Retrovir	300 mg/ bid	Bone marrow suppression Anemia and/or neutropenia Subjective complaints : GI intolerance, headache, insomnia, asthenia
Didanosine (ddI)	Videx	> 60 kg : 200 mg/ bid < 60 kg : 125 mg/ bid	Pancreatitis Periphernal neuropathy, Nausea, diarrhea
Zalcitabine (ddC)	HIVID	0.75 mg/ tid	Peripheral neuropathy Stomatitis
Stavudine (d4T)	Zerit	> 60 kg : 40 mg/ bid < 60 kg : 30 mg/ bid	Peripheral neuropathy
Lamivudine (3TC)	Epivir	150 mg/ bid < 50 kg : 2 mg/kg/ bid	Minimal toxicity
Non nucleoside reverse transcriptase inhibitors (NNRTIS)			
Nevirapine	Viramune	200 mg po qd x 14 days then 200 mg po bid	Rash, increased transaminase levels, hepatitis
Delavirdine	Rescriptor	400 mg po tid (four 100 mg tabs in > 3 oz water to produce slurry)	Rash, headache
Protease inhibitors			
Indinavir	Crixivan	800 mg q 8 h take 1 h before or 2 h after meals, may take with skim milk or low fat meal	Nephrolithiasis, GI intolerance, nausea, Lab: increased indirect bilirubinemia (inconsequential) Misc : headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia

Table 5 (cont.) Dosing recommendation and adverse effect of NRTIS, NNRTIS and protease inhibitors

Protease inhibitors (continue)			
Generic name	Trade name	Dosing recommendation	Adverse effects
Ritonavir	Norvir	600 mg q 12 h take with food if possible	GI intolerance, nausea, vomiting, diarrhea, Paresthesias (circumoral and extremities) Hepatitis, asthenia Taste perversion Lab: triglycerides increase >200%, transaminase elevation, elevated CPK and uric acid
Saquinavir	Invirase	600 mg tid take with large meal	GI intolerance, nausea, diarrhea. Headache Elevated transaminase enzymes
Nelfinavir	Viracept	750 mg tid take with food (meal or light snack)	Diarrhea

Table 6 Drug Interactions between protease inhibitors and other drugs

Drugs interactions requiring dose modifications				
	Indinavir	Ritonavir	Saquinavir	Nelfinavir
Fluconazole	No dose change	No dose change	No data	No dose change
Ketoconazole and Itraconazole	Decrease dose to 600 mg q 8 h	Increase ketoconazole >3 fold; dose adjustment required	Increase saquinavir levels 3 fold; no dose change	No dose change
Rifabutin	Reduce rifabutin to half dose: 150 mg qd	Consider alternative drug	Not recommended	Reduce rifabutin to half dose : 150 mg qd
Rifampin	Contraindicated	Unknown*	Not recommended	Not recommended
Oral Contraceptives	Modest increase Ortho-Novum levels; no dose change	Ethinyl estradiol levels decreased; use alternative or additional contraceptive method	No data	Ethinyl estradiol and norethindrone levels decreased; use alternative or additional contraceptive method
Miscellaneous	Grapefruit juice reduces indinavir levels by 26%	Desipramine increased 145% : reduce dose, theophylline levels decreased: dose increase	Grapefruit juice increases saquinavir levels	

*Rifampin reduces ritonavir 35%. Increase ritonavir dose or use of ritonavir in combination therapy is strongly recommended. The effect of ritonavir on rifampin is unknown. Used concurrently, there may be increased liver toxicity. Therefore, patients on ritonavir and rifampin should be monitored closely.

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