VIRGINIA
EPIDEMIOLOGY BULLETIN

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Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*

The following article includes excerpts from the MMWR article with the above title (1998;47[No. RR-5]:1-82). If you would like to receive a copy of the entire MMWR article, you may call the Office of Epidemiology at 804/786-6261 or visit the Centers for Disease Control and Prevention web site at http://www.cdc.gov.

INTRODUCTION

These guidelines were developed by the Panel on Clinical Practices for Treatment of HIV Infection, convened by the Department of Health and Human Services and the Henry J. Kaiser Family Foundation. The guidelines contain recommendations for the clinical use of antiretroviral agents in the treatment of adults and adolescents who are infected with the human immunodeficiency virus (HIV). Guidance for the use of antiretroviral treatment in pediatric HIV infection is not contained in this report.

These guidelines are intended for use by physicians and other health-care providers who use antiretroviral therapy to treat HIV-infected adults and adolescents. The recommendations contained herein are presented in the context of and with reference to Principles of Therapy for HIV Infection, formulated by the National Institutes of Health (NIH) Panel to Define Principles of Therapy of HIV Infection (Summary on page 5).

This report addresses the following issues: the use of testing for plasma HIV RNA levels (viral load) and CD4+ T cell count; initiating therapy in established HIV infection; initiating therapy in patients who have advanced-stage HIV disease; interruption of antiretroviral therapy; changing therapy and available therapeutic options; the treatment of acute HIV infection; antiretroviral therapy in adolescents; and antiretroviral therapy in the pregnant woman.

USE OF TESTING FOR PLASMA HIV RNA LEVELS AND CD4+ T CELL COUNT IN GUIDING DECISIONS FOR THERAPY

Decisions regarding either initiating or changing antiretroviral therapy should be guided by monitoring the laboratory parameters of both plasma HIV RNA and CD4+ T cell count and by assessing the clinical condition of the patient. Results of these two laboratory tests provide the physician with important information about the virologic and immunologic status of the patient and the risk of disease progression to acquired immunodeficiency syndrome (AIDS).

The consensus of the Panel is that viral load testing is the essential parameter in decisions to initiate or change antiretroviral therapies. Measurement of plasma HIV RNA levels, using quantitative methods, should be performed at the time of diagnosis of HIV infection and every 3-4 months thereafter in the untreated patient (Table 1). CD4+ T cell counts should be measured at the time of diagnosis and generally every 3-6 months thereafter. These intervals between tests are merely recommendations, and flexibility should be exercised according to the circumstances of the individual case. Plasma HIV RNA levels also should be measured immediately prior to and again at 4-8 weeks after initiation of antiretroviral therapy. This second time point allows the clinician to evaluate the initial effectiveness of therapy because in most patients, adherence to a regimen of potent antiretroviral agents should result in a large decrease (~0.5 to 0.75 $\log_{10}$) in viral load by 4-8 weeks. The viral load should continue to decline over the following weeks, and in most persons it

**Information included in these guidelines may not represent Food and Drug Administration (FDA) approval or approved labeling for the particular products or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with the FDA-defined legal standards for product approval.*

Table 1. Indications for plasma HIV RNA testing*

Clinical Indication	Information	Use
Syndrome consistent with acute HIV infection	Established diagnosis when HIV antibody test is negative or indeterminate	Diagnosis†
Initial evaluation of newly diagnosed HIV infection	Baseline viral load "set point"	Decision to start or defer therapy
Every 3-4 months in patients not on therapy	Changes in viral load	Decision to start therapy
4-8 weeks after initiation of antiretroviral therapy	Initial assessment of drug efficacy	Decision to continue or change therapy
3-4 months after start of therapy	Maximal effect of therapy	Decision to continue or change therapy
Every 3-4 months in patients on therapy	Durability of antiretroviral effect	Decision to continue or change therapy
Clinical event or significant decline in CD4+ T cells	Association with changing or stable viral load	Decision to continue, initiate, or change therapy

**Acute illness (e.g., bacterial pneumonia, tuberculosis, HSV, PCP) and immunizations can cause increases in plasma HIV RNA for 2-4 weeks; viral load testing should not be performed during this time. Plasma HIV RNA results should usually be verified with a repeat determination before starting or making changes in therapy. HIV RNA should be measured using the same laboratory and the same assay.*
†Diagnosis of HIV infection determined by HIV RNA testing should be confirmed by standard methods (e.g., Western blot serology) performed 2-4 months after the initial indeterminate or negative test.

becomes below detectable levels (currently defined as <500 RNA copies /mL) by 12-16 weeks of therapy. The speed of viral load decline and the movement toward undetectable are affected by the baseline CD4+ T cell count, the initial viral load, potency of the regimen, adherence, prior exposure to antiretroviral agents, and the presence of any opportunistic infections. These individual differences must be considered when monitoring the effect of therapy. However, the absence of a virologic response of the magnitude previously described (i.e., ~0.5 to 0.75 $\log_{10}$ by 4-8 weeks and undetectable by 12-16 weeks) should prompt the physician to reassess patient adherence, rule out malabsorption, consider repeat RNA testing to document lack of response, and/or consider a change in drug regimen. Once the patient is on therapy, HIV RNA testing should be repeated every 3-4 months to evaluate the continuing effectiveness of therapy. Because differences exist among commercially available tests, confirmatory plasma HIV RNA levels should be measured by the same laboratory using the same technique to ensure consistent results.

A substantial change in plasma viremia is considered to be a threefold or 0.5 $\log_{10}$ increase or decrease. A substantial decrease in CD4+ T cell count is a decrease of >30% from baseline for absolute cell numbers and a decrease of >3% from baseline in percentages of cells. Viral load and trends in viral load are considered more informative for guiding decisions regarding antiretroviral therapy than are CD4+ T cell counts. However, exceptions to this rule do occur; when changes in viral loads and CD4+ T cell counts are discordant, expert consultation should be considered.

ESTABLISHED HIV INFECTION

Patients who have established HIV infection are considered in two arbitrarily defined clinical categories: 1) asymptomatic infection or 2) symptomatic disease (e.g., 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. Before initiating therapy in any patient, the following evaluation should be performed:

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

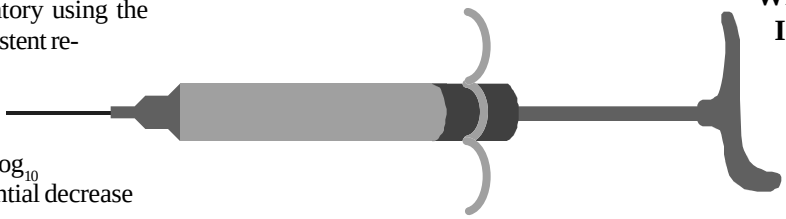
Additional evaluation should include routine tests pertinent to the prevention of opportunistic infections, if not already performed (i.e., VDRL, tuberculin skin test, toxoplasma IgG serology, and gynecologic exam with Pap smear), and other tests as clinically indicated (e.g., chest radiograph, hepatitis C virus serology, and ophthalmologic exam).

Considerations for Initiating Therapy in the Patient Who Has Asymptomatic HIV Infection

It has been demonstrated that antiretroviral therapy provides clinical benefit in HIV-infected persons who have advanced HIV disease and immunosuppression. Although there is theoretical benefit to treating patients who have CD4+ T cells >500 cells/mm^3, no long-term clinical benefit of treatment has yet been demonstrated. A major dilemma confronting patients and practitioners is that the antiretroviral regimens currently available that have the greatest potency in terms of viral suppression and CD4+ T cell preservation are medically complex, are associated with several specific side effects and drug interactions, and pose a substantial challenge for adherence.

The physician and the asymptomatic patient must consider multiple risks and benefits in deciding when to initiate therapy (Table 2). Thus, the decision to begin therapy in the asymptomatic patient is complex and must be made in the setting of careful patient counseling and education. The factors that must be considered in this decision include the following: 1) the willingness of the individual to begin therapy; 2) the degree of existing immunodeficiency as determined by the CD4+ T cell count; 3) the risk for disease progression as determined by the level of plasma HIV RNA; 4) the potential benefits and risks of initiating therapy in asymptomatic persons, as discussed above; and 5) the likelihood, after counseling and education, of adherence to the prescribed treatment regimen.

Initiating Therapy in the Patient Who Has Asymptomatic HIV Infection



Once the patient and physician have decided to initiate antiretroviral therapy, treatment should be aggressive, with the goal of maxi-

Table 2. 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

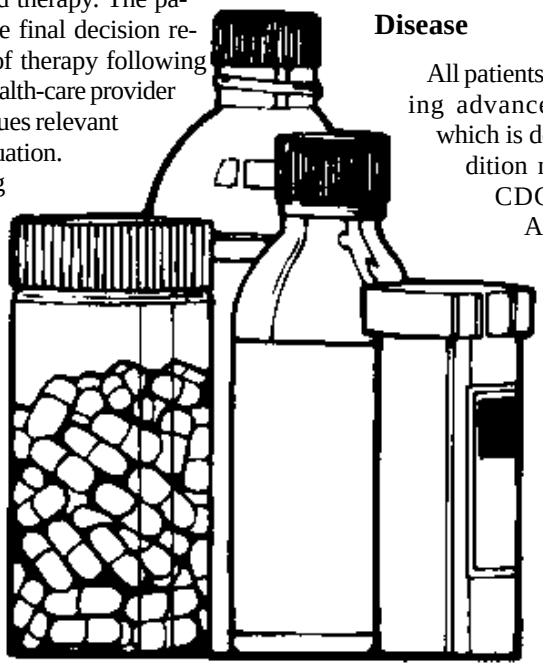
Unknown long-term toxicity of antiretroviral drugs

Unknown duration of effectiveness of current antiretroviral therapies

mal suppression of plasma viral load to undetectable levels (Tables 3 and 4). In general, any patient who has <500 CD4+ T cells/mm^3 or >10,000 branched DNA (bDNA) or 20,000 reverse transcriptase polymerase chain reaction (RT-PCR) copies of HIV RNA/mL of plasma should be offered therapy. However, the strength of the recommendation for therapy should be based on the readiness of the patient for treatment and a consideration of the prognosis for risk for progression to AIDS as determined by viral load, CD4+ T cell count, and the slope of the CD4+ T cell count decline.

Currently, there are two general approaches to initiating therapy in the asymptomatic patient: 1) a therapeutically more aggressive approach in which most patients would be treated early in the course of HIV infection due to the recognition that HIV disease is virtually always progressive and 2) a therapeutically more cautious approach in which therapy may be delayed because the balance of the risk for clinically significant progression and other factors discussed above are considered to weigh in favor of observation and delayed therapy. The patient should make the final decision regarding acceptance of therapy following discussion with the health-care provider regarding specific issues relevant to his own clinical situation.

When initiating therapy in the patient who has never been administered antiretroviral therapy, one should begin with a regimen that is expected to reduce viral replication to undetectable levels. Based on the weight of experience, the preferred regimen to accomplish this consists of two nucleoside reverse transcriptase inhibitors (NRTIs) and one potent protease inhibitor (PI). 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.



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.

Initiating Therapy in Patients Who Have Advanced-Stage HIV Disease

All patients diagnosed as having 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 who have symptomatic HIV infection without AIDS, defined as the presence of thrush or unexplained fever, also should be treated.

Special Considerations in the Patient Who Has Advanced-Stage HIV Disease

Some patients with opportunistic infections, wasting, dementia, or malignancy are first diagnosed with HIV infection at this advanced stage of disease. All patients who have advanced HIV disease should be treated with antiretroviral therapy. When the patient is acutely ill with an opportunistic infection or

Table 3. Indications for the initiation of antiretroviral therapy

Clinical Category	CD4+ T cell count and HIV RNA	Recommendation
Symptomatic (i.e., AIDS, thrush, unexplained fever)	Any value	Treat
Asymptomatic	CD4+ T cells <500/mm^3 **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 and willingness of the patient to accept therapy.*
Asymptomatic	CD4+ T cells >500/mm^3 **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 whose CD4+ T cell counts are between 350-500/mm^3 and HIV RNA levels <10,000 (bDNA) or <20,000 (RT-PCR).*

Table 4. Recommended antiretroviral agents for treatment of established HIV infection

Preferred: Strong evidence of clinical benefit and/or sustained suppression of plasma viral load. One choice each from column A and column B. Drugs are listed in random, not priority, order:

Column A	Column B
Indinavir	ZDV + ddl
Nelfinavir	d4T + ddl
Ritonavir	ZDV + ddC
Saquinavir- SGC*	ZDV + 3TC§
Ritonavir + Saquinavir-SGC or HGC†	d4T + 3TC§

Alternative: Less likely to provide sustained virus suppression;
1 NNRTI (Nevirapine)¶ + 2 NRTIs (Column B, above)
Saquinavir-HGC + 2 NRTIs (Column B, above)

Not generally recommended: Strong evidence of clinical benefit, but initial virus suppression is not sustained in most patients
2 NRTIs (Column B, above)

Not recommended:** Evidence against use, virologically undesirable, or overlapping toxicities

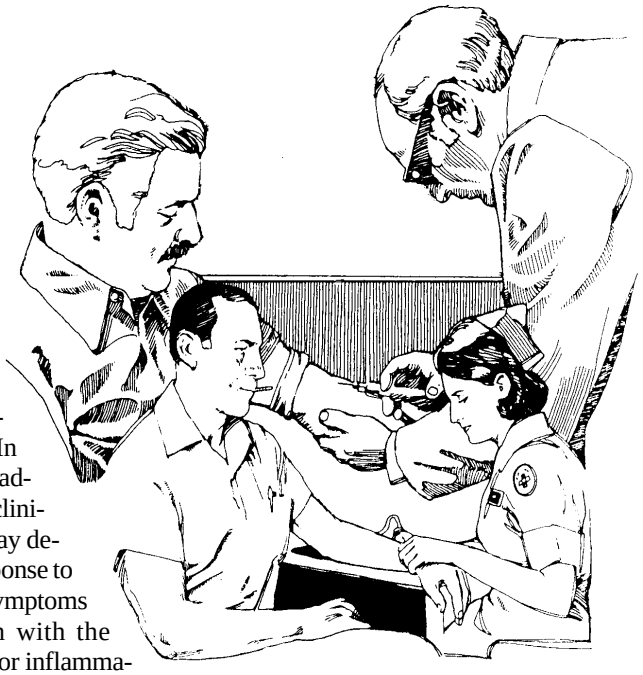
All monotherapies	d4T + ZDV	ddC + ddl
ddC+ d4T	ddC + 3TC	

**Virologic data and clinical experience with saquinavir-sgc are limited in comparison with other protease inhibitors.*
†Use of ritonavir 400 mg b.i.d. with saquinavir soft-gel formulation (Fortovase™) 400 mg b.i.d. results in similar areas under the curve (AUC) of drug and antiretroviral activity as when using 400 mg b.i.d. of Invirase™ in combination with ritonavir. However, this combination with Fortovase™ has not been extensively studied and gastrointestinal toxicity may be greater when using Fortovase™.
§High-level resistance to 3TC develops within 2-4 wks. in partially suppressive regimens; optimal use is in three-drug antiretroviral combinations that reduce viral load to <500 copies/mL.
¶The only combination of 2 NRTIs + 1 NNRTI that has been shown to suppress viremia to undetectable levels in the majority of patients is ZDV+ddl+Nevirapine. This combination was studied in antiretroviral-naive persons.
***ZDV monotherapy may be considered for prophylactic use in pregnant women who have low viral load and high CD4+ T cell counts to prevent perinatal transmission.*

other complication of HIV infection, the clinician should consider clinical issues (e.g., 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 (e.g., two NRTIs and a PI) should be used (Table 4). Advanced-stage patients being maintained on an antiretroviral regimen should not have the therapy discontinued during an acute opportunistic infection or malignancy, unless concerns exist regarding drug toxicity, intolerance, or drug interactions.

Patients who have progressed to AIDS often are treated with complicated combinations of drugs, and the clinician and patient should be alert to the potential for multiple drug interactions. Thus, the choice of which antiretroviral agents to use must be made with consideration given to potential drug interactions and overlapping drug toxicities. Health-care providers should inform their patients of the need to discuss any new drugs, including over-the- counter agents and alternative medications, that they may consider taking, and careful attention should be given to the relative risk versus benefits of specific combinations of agents.

Initiation of potent antiretroviral therapy often is associated with some degree of recovery of immune function. In this setting, patients who have advanced HIV disease and subclinical opportunistic infections may develop a new immunologic response to the pathogen, and, thus, new symptoms may develop in association with the heightened immunologic and/or inflammatory response. This should not be interpreted as a failure of antiretroviral therapy, and these newly presenting opportunistic infections should be treated appropriately while maintaining the patient on the antiretroviral regimen. Viral load measurement is helpful in clarifying this association.



INTERRUPTION OF ANTIRETROVIRAL THERAPY

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 currently available studies and therefore 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 any antiretroviral medication has to be discontinued for an extended time, clinicians and patients should be aware 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.

CHANGING A FAILING REGIMEN

Considerations for Changing a Failing Regimen

The decision to change regimens should be approached with careful consideration of several complex factors. These factors include

recent clinical history and physical examination; plasma HIV RNA levels measured on two separate occasions; absolute CD4+ T cell count and changes in these counts; remaining treatment options in terms of potency, potential resistance patterns from prior antiretroviral therapies, and potential for adherence/tolerance; assessment of adherence to medications; and psychological preparation of the patient for the implications of the new regimen (e.g., side effects, drug interactions, dietary requirements and possible need to alter concomitant medications).

It is important to distinguish between the need to change therapy because of drug failure versus drug toxicity. In the latter case, it is appropriate to substitute one or more alternative drugs of the same potency and from the same class of agents as the agent suspected to be causing the toxicity. In the case of drug failure where more than one drug had been used, a detailed history of current and past antiretroviral medications, as well as other HIV-related medications, should be obtained. Optimally and when possible, the regimen should be changed entirely to drugs that have not been taken previously. With triple combinations of drugs, at least two and preferably three new drugs must be used; this recommendation is based on the current understanding of strategies to prevent drug resistance.

The following three categories of patients should be considered with regard to a change in therapy: persons who are receiving incompletely suppressive antiretroviral therapy with single or double nucleoside therapy and with detectable or undetectable plasma viral load; persons who have been on potent combination therapy, including a PI, and whose viremia was initially suppressed to undetectable levels but has again become detectable; and persons who have been on potent combination therapy, including a PI, and whose viremia was never suppressed to below detectable limits.

Summary of the Principles of Therapy of HIV Infection

1. Ongoing HIV replication leads to immune system damage and progression to AIDS. HIV infection is always harmful, and true long-term survival free of clinically significant immune dysfunction is unusual.
2. Plasma HIV RNA levels indicate the magnitude of HIV replication and its associated rate of CD4+ T cell destruction, whereas CD4+ T cell counts indicate the extent of HIV-induced immune damage already suffered. Regular, periodic measurement of plasma HIV RNA levels and CD4+ T cell counts is necessary to determine the risk for disease progression in an HIV-infected person and to determine when to initiate or modify antiretroviral treatment regimens.
3. As rates of disease progression differ among HIV-infected persons, treatment decisions should be individualized by level of risk indicated by plasma HIV RNA levels and CD4+ T cell counts.
4. The use of potent combination antiretroviral therapy to suppress HIV replication to below the levels of detection of sensitive plasma HIV RNA assays limits the potential for selection of antiretroviral-resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay disease progression. Therefore, maximum achievable suppression of HIV replication should be the goal of therapy.
5. The most effective means to accomplish durable suppression of HIV replication is the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents with which the patient has been treated previously.
6. Each of the antiretroviral drugs used in combination therapy regimens should always be used according to optimum schedules and dosages.
7. The available effective antiretroviral drugs are limited in number and mechanism of action, and cross-resistance between specific drugs has been documented. Therefore, any change in antiretroviral therapy increases future therapeutic constraints.
8. Women should receive optimal antiretroviral therapy regardless of pregnancy status.
9. The same principles of antiretroviral therapy apply to HIV-infected children, adolescents, and adults, although the treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.
10. Persons identified during acute primary HIV infection should be treated with combination antiretroviral therapy to suppress virus replication to levels below the limit of detection of sensitive plasma HIV RNA assays.
11. HIV-infected persons, even those whose viral loads are below detectable limits, should be considered infectious. Therefore, they should be counseled to avoid sexual and drug-use behaviors that are associated with either transmission or acquisition of HIV and other infectious pathogens.

Criteria for Changing Therapy

Specific criteria that should prompt consideration for changing therapy include the following:

- Less than a 0.5-0.75 log reduction in plasma HIV RNA by 4-8 weeks following initiation of therapy.
- Failure to suppress plasma HIV RNA to undetectable levels within 4-6 months of initiating therapy.
- Repeated detection of virus in plasma after initial suppression to undetectable levels, suggesting the development of resistance.
- Any reproducible significant increase, defined as threefold or greater from the nadir of plasma HIV RNA not attributable to intercurrent infection, vaccination, or test methodology except as noted above.
- Undetectable viremia in the patient who is being administered double nucleoside therapy.
- Persistently declining CD4+ T cell numbers, as measured on at least two separate occasions.
- Clinical deterioration.

A final consideration in the decision to change therapy is the recognition of the still limited choice of available agents and the knowledge that a decision to change may reduce future treatment options for the patient. It is recommended that the decision to change therapy and design a new regimen should be made with assistance from a clinician experienced in the treatment of HIV infected patients through consultation or referral.

ACUTE HIV INFECTION

Considerations for Treatment of Patients with Acute HIV Infection

Information regarding treatment of acute HIV infection from clinical trials is limited. There is evidence for a short-term effect of therapy on viral load and CD4+ T cell counts, but there are as yet no outcome data demon-

strating a clinical benefit of antiretroviral treatment of primary HIV infection. Ongoing clinical trials are addressing the question of the long-term clinical benefit of more potent treatment regimens.

The theoretical rationale for early intervention is fourfold:

- To suppress the initial burst of viral replication and decrease the magnitude of virus dissemination throughout the body;
- To decrease the severity of acute disease;
- To potentially alter the initial viral "set-point", which may ultimately affect the rate of disease progression;
- To possibly reduce the rate of viral mutation due to the suppression of viral replication.

No patient should be treated for HIV infection until the infection is documented, except in the setting of postexposure prophylaxis of health-care workers with antiretroviral agents.

Treatment Regimen for Primary HIV Infection

Once the physician and patient have decided to use antiretroviral therapy for primary 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 NRTIs and one potent PI. Any regimen that is not expected to maximally suppress viral replication is not considered appropriate for treating the acutely HIV-infected person.

Testing for plasma HIV RNA levels and CD4+ T cell count and toxicity monitoring should be performed as previously described, that is, on initiation of therapy, after 4 weeks, and every 3-4 months thereafter (Table 1).

Acute retroviral syndrome: associated signs and symptoms and 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%)
  - Meningoencephatitis or aseptic meningitis
  - Peripheral neuropathy or radiculopathy
  - Facial palsy
  - Guillain-Barré syndrome
  - Brachial neuritis
  - Cognitive impairment or psychosis

**Adapted from Niu MJ, Stein D, Schnittman SM. Primary human immunodeficiency virus type 1 infection: review of pathogenesis and early treatment intervention in humans and animal retrovirus infections.* J Infect Dis *1993;168:1490-501.*

Duration of Therapy for Primary HIV Infection

The optimal duration and composition of therapy are unknown, and ongoing clinical trials are expected to provide data relevant to these issues. The difficulties inherent in determining the optimal duration and composition of therapy initiated for acute infection should be considered when first counseling the patient regarding therapy.

CONSIDERATIONS FOR ANTIRETROVIRAL THERAPY IN THE HIV-INFECTED ADOLESCENT

HIV-infected adolescents who were infected through sexual contact or through injecting-drug use during adolescence appear to follow a clinical course that is more similar to HIV disease in adults than in children. In contrast, adolescents who were infected perinatally or through blood products as young children have a unique clinical course that may differ from other adolescents and long-term surviving adults. Currently, most HIV-infected adolescents were infected through sexual contact during the adolescent period and are in a relatively early stage of infection, making them ideal candidates for early intervention.

It is currently recommended that medications used to treat HIV and opportunistic infections in adolescents should be administered in a dosage based on Tanner staging of puberty and not specific age. Adolescents in early puberty (Tanner I-II) should receive doses as recommended in the pediatric guidelines, whereas those in late puberty (Tanner V) should receive doses recommended in the adult guidelines. Youth who are in the midst of their growth spurt (Tanner III females and Tanner IV males) should be closely monitored for medication efficacy and toxicity when choosing adult or pediatric dosing guidelines.

CONSIDERATIONS FOR ANTIRETROVIRAL THERAPY IN THE PREGNANT HIV-INFECTED WOMAN

Guidelines for optimal antiretroviral therapy and for initiation of therapy in pregnant HIV-infected women should be the same as those delineated for nonpregnant adults. Thus, the woman's clinical, virologic, and immunologic status should be the primary factor in guiding treatment decisions. However, it must be realized that the potential impact of such therapy on the fetus and infant is unknown. The decision to use any antiretroviral drug during pregnancy should be made by the

woman following discussion with her health-care provider regarding the known and unknown benefits and risks to her and her fetus. Long-term follow-up is recommended for all infants born to women who have received antiretroviral drugs during pregnancy.

Women who are in the first trimester of pregnancy and who are not receiving antiretroviral therapy may wish to consider delaying initiation of therapy until after 10-12 weeks' gestation because this is the period of organogenesis when the embryo is most susceptible to potential teratogenic effects of drugs; the risks of antiretroviral therapy to the fetus during that period are unknown. Some women already receiving antiretroviral therapy may have their pregnancy diagnosed early enough in gestation that concern for potential teratogenicity may lead them to consider temporarily stopping antiretroviral therapy until after the first trimester. Insufficient data exist that either support or refute teratogenic risk of antiretroviral drugs when administered during the first 10-12 weeks' gestation. However, a rebound in viral levels would be anticipated during the period of discontinuation, and this rebound could theoretically be associated with increased risk of early in utero HIV transmission or could potentiate disease progression in the woman. If antiretroviral therapy is discontinued during the first trimester for any reason, all agents should be stopped simultaneously to avoid development of resistance. Once the drugs are reinstituted, they should be introduced simultaneously for the same reason.

Currently, minimal data are available regarding the pharmacokinetics and safety of antiretroviral agents during pregnancy for drugs other than zidovudine (ZDV). In the absence of data, drug choice needs to be individualized based on discussion with the patient and available data from preclinical and clinical testing of the individual drugs. Although studies of combination therapy with PIs in pregnant HIV-infected women are in progress, no data are currently available regarding drug dosage, safety and tolerance during pregnancy.

Transmission of HIV from mother to infant can occur at all levels of maternal HIV RNA. To date, the only drug that has been shown to reduce the risk of perinatal HIV transmission is ZDV when administered according to the following regimen: orally administered antenatally after 14 weeks' gestation and continued throughout pregnancy, intravenously administered during the intrapartum period, and administered orally to the newborn for the first 6 weeks of life. This chemoprophylactic regimen was shown to reduce the risk for perinatal transmission by 66% in a randomized, double-blind clinical trial. Insufficient data are available to justify the substitution of any antiretroviral agent other than ZDV to reduce perinatal HIV transmission; further research should address this question. For the time being, if combination antiretroviral drugs are administered to the pregnant woman for treatment of her HIV infection, ZDV should be included as a component of the antenatal therapeutic regimen whenever possible, and the intrapartum and neonatal ZDV components of the chemoprophylactic regimen should be administered to reduce the risk for perinatal transmission.

The time-limited use of ZDV alone during pregnancy for chemoprophylaxis of perinatal transmission is controversial. The potential benefits of standard combination antiretroviral regimens for treatment of HIV infection should be discussed with and offered to all pregnant HIV-infected women. For women who have more advanced disease and/or higher levels of HIV RNA, concerns about resistance are greater and these women should be counseled that a combination antiretroviral regimen that includes ZDV for reducing transmission risk would be more optimal for their own health than use of ZDV chemoprophylaxis alone.

Health-care providers who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to antiretroviral drugs to the Antiretroviral Pregnancy Registry. The registry collects observational, nonexperimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing potential teratogenicity. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The registry is a collaborative project with an advisory committee of obstetric and pediatric practitioners, staff from CDC and NIH, and staff from pharmaceutical manufacturers. The registry allows the anonymity of patients, and birth outcome follow-up is obtained by registry staff from the reporting physician. Referrals should be directed to Antiretroviral Pregnancy Registry, Post Office Box 13398, Research Triangle Park, NC 27709-3398; telephone (800) 258-4263.

CONCLUSION

The Panel has attempted to use the advances in current understanding of the pathogenesis of HIV in the infected person to translate scientific principles and data obtained from clinical experience into recommendations that can be used by the clinician and patient to make therapeutic decisions. The recommendations are offered in the context of an ongoing dialogue between the patient and the clinician after having defined specific therapeutic goals with an acknowledgment of uncertainties. It is necessary for the patient to receive a continuum of medical care and services, including social, psychosocial, and nutritional services, with the availability of expert referral and consultation. To achieve the maximal flexibility in tailoring therapy to each patient over the duration of his or her infection, it is imperative that drug formularies allow for all FDA-approved NRTI, non-nucleoside reverse transcriptase inhibitors, and PI as treatment options. The Panel strongly urges industry and the public and private sectors to conduct further studies to allow refinement of these guidelines. Specifically, studies are needed to optimize recommendations for first-line therapy; to define second-line therapy; and to more clearly delineate the reasons for treatment failure. The Panel remains committed to revising their recommendations as such new data become available.

CDC WONDER System Changing from PC/DOS to World Wide Web

Effective January 1, 2000, CDC WONDER in the DOS version with its e-mail communications will no longer be available. CDC WONDER will only be accessible on the World Wide Web at http:\\wonder.cdc.gov.

Notification of this change has been sent to all users through the CDC WONDER e-mail system. Present users of WONDER/PC e-mail will need access to another e-mail system by the year 2000.

For more information detailing the upcoming changes, the reasons behind them and suggestions for alternate e-mail services, please check your WONDER/PC mail or call the WONDER Customer Support at 888/496-8347.

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, May 1998						Total Cases Reported Statewide, January through May		
	State	Regions					This Year	Last Year	5 Yr Avg
		NW	N	SW	C	E			
AIDS	54	7	11	2	15	19	333	490	546
Campylobacteriosis	56	9	15	13	9	10	193	155	174
Giardiasis	40	1	15	5	3	16	141	172	115
Gonorrhea	330	4	37	18	82	189	2425	3343	4300
Hepatitis A	29	1	15	1	3	9	115	74	66
Hepatitis B	15	1	3	0	2	9	45	50	52
Hepatitis NANB	2	1	0	0	0	1	3	8	11
HIV Infection	63	6	13	7	20	17	375	399	350
Influenza	2	2	0	0	0	0	1034	438	624
Legionellosis	0	0	0	0	0	0	4	9	6
Lyme Disease	6	0	0	1	3	2	10	0	10
Measles	0	0	0	0	0	0	2	0	1
Meningitis, Aseptic	12	2	3	1	0	6	46	70	66
Meningitis, Bacterial†	6	1	2	0	0	3	26	36	42
Meningococcal Infections	3	1	0	1	0	1	20	29	28
Mumps	0	0	0	0	0	0	4	4	12
Pertussis	0	0	0	0	0	0	6	19	11
Rabies in Animals	61	17	16	10	8	10	261	261	192
Rocky Mountain Spotted Fever	0	0	0	0	0	0	0	2	1
Rubella	0	0	0	0	0	0	0	1	0
Salmonellosis	91	12	23	11	34	11	301	291	311
Shigellosis	17	1	5	0	0	11	54	219	170
Syphilis, Early‡	15	1	1	4	6	3	189	278	466
Tuberculosis	26	3	8	0	2	13	118	140	136

Localities Reporting Animal Rabies This Month: Accomack 1 raccoon; Amherst 1 raccoon, 1 skunk; Arlington 1 bat; Bedford 2 raccoons; Campbell 1 raccoon; Charlotte 1 groundhog, 1 raccoon; Culpeper 1 raccoon; Fairfax 2 bats, 2 foxes, 1 groundhog, 6 raccoons, 1 skunk; Hanover 1 raccoon, 1 skunk; James City 1 raccoon; King & Queen 1 skunk; Loudoun 1 fox, 2 raccoons; Madison 1 raccoon; Mecklenburg 1 raccoon; Montgomery 1 skunk; Nelson 2 raccoons; Newport News 1 raccoon; Northampton 2 raccoons; Northumberland 2 raccoons; Orange 1 fox, 1 raccoon; Page 1 raccoon, 1 skunk; Pittsylvania 1 dog, 1 raccoon; Portsmouth 1 raccoon; Prince George 2 raccoons; Richmond City 1 raccoon; Spotsylvania 1 fox, 1 raccoon; Stafford 1 bat, 1 cat, 1 raccoon, 2 skunks; Tazewell 1 raccoon; Virginia Beach 1 raccoon; Warren 1 raccoon; Washington 1 fox.

Occupational Illnesses: Asbestosis 33; Carpal Tunnel Syndrome 54; DeQuervain's Syndrome 1; Hearing Loss 17; Lead Poisoning 1; Pneumoconiosis 23.

*Data for 1998 are provisional. †Other than meningococcal. ‡Includes primary, secondary, and early latent.

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