

Human Immunodeficiency Virus Infection: 2002 Sourcebook for the Healthcare Clinician

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This sourcebook was made possible through funding to the Mountain Plains Regional AIDS Education and Training Center from the United States Department of Health and Human Services, Public Health Service, Health Resources and Services Administration grant # 1H4A HA 00064-01.

The Mountain Plains Regional AIDS Education and Training Center affiliated states participating in the development and distribution of this sourcebook include Colorado, Kansas, Nebraska, New Mexico, North Dakota, South Dakota, Utah, and Wyoming.



Table of Contents

Introduction	.1
Considerations for Primary Care	.1
Basic Overview	.2
Pathophysiology of HIV Infection	.2
Risk Assessment and Harm Reduction	.3
Identifying Risk	.3
Reducing Risk	.5
Occupational Exposure to HIV	.6
Diagnosing HIV Infection	.6
Treatment	.7
Clinical Assessment	.7
Antiretroviral Therapy (ART)	.10
Symptom Evaluation in the HIV-infected Patient	.14
Pulmonary Manifestations	.14
Nervous System Presentations	.15
Ocular Involvement	.17
Cutaneous Manifestations	.17
Oral Health Care	.18
Metabolic Complications	.18
Prophylaxis against Secondary Infection	.21
<i>Pneumocystis carinii</i> pneumonia	.21
Varicella Zoster and Herpes Simplex	.22
Mycobacterium Avium-Complex	.22
Tuberculosis	.22
Toxoplasmosis	.22
Immunizations	.23
Women and HIV	.23
Epidemiology	.23
Clinical Manifestations	.24
Pregnancy	.24
Psychosocial Issues in the Care of the HIV-Infected Patient	.24
Appendix A: Postexposure Prophylaxis	.26
Appendix B: Current Antiretroviral Agents	.30
Resources	.33
National AIDS Services, Hotlines, and On-Line Resources	.33
MPAETC E-Mail Consultation Service for HIV Infection	.34
Patient Assistance Programs for HIV Medications	.35
Bibliography	.36
Roster of National AIDS Education and Training Centers	.38
State Specific Resources	.41

Introduction

This edition of *Human Immunodeficiency Virus Infection: 2002 Sourcebook for the Healthcare Clinician* provides information about HIV infection and AIDS for clinicians who work in today's health care system. It will be useful to many kinds of clinicians, including physicians, physician assistants, nurses, nurse practitioners, nurse midwives, pharmacists, dentists, dental hygienists, social workers, mental health counselors, case managers, and others. The sourcebook contains an outline of basic patient care in HIV infection, plus a list of resources that can be easily accessed in the local setting. It is not presented as a textbook on HIV infection, but rather, as a handy reference for some of the practical problems encountered in daily practice.

Any recommendations made herein should not be interpreted as "practice guidelines" or a "standard of care" that the clinician must follow in order to be considered competent, although the information is derived from and/or based on current treatment, prophylaxis, and prevention guidelines. The authors have no authority to develop any such formalized approach to care of patients with HIV infection. As with any health care intervention, the patient's individual needs are paramount. And, as with any difficult-to-treat condition, clinicians are encouraged to consult with and refer to specialists in the field as needed.

This sourcebook cites guidelines and recommendations related to antiretroviral therapy (ART), treatment of opportunistic disease, HIV testing and counseling, prevention of perinatal transmission, and post exposure prophylaxis (PEP). Reference publications may be obtained from any of the AIDS Education and Training Centers (AETC), the Centers for Disease Control and Prevention (CDC), HIV/AIDS Treatment Information Service (HIVATIS), or the National AIDS Clearinghouse. Complete information for accessing these resources is provided in the resource section of this book.

Considerations for Primary Care

The HIV epidemic presents challenges and opportunities for primary care practitioners. HIV is a chronic infection with complex and frequently changing care considerations. Like most chronic conditions, health care needs are exacerbated by social, economic, and mental health conditions. Education and prevention are key factors in the continuum of care. Table 1 lists primary care activities in HIV infection.

Table 1. Primary Care Activities in HIV Disease

- Provide prevention education
- Evaluate risk for HIV infection
- Counsel at-risk patients about HIV antibody testing
- Refer to risk-reducing and social service programs as needed
- Diagnose HIV infection as early as possible
- Evaluate baseline disease stage and clinical condition
- Encourage health-promoting behaviors
- Prevent further spread of HIV infection
- Assess social and emotional support and arrange referrals as needed
- Encourage adherence to treatment

With appropriate consultations and referrals:

- Support antiretroviral therapy
- Manage troublesome symptoms - diarrhea, vomiting, fever, weight loss, metabolic complications, etc.
- Administer prophylaxis against opportunistic diseases as recommended
- Monitor for complications of ART, signs and symptoms of opportunistic infection, or other problems requiring urgent intervention

Primary care clinicians have major responsibilities in the HIV epidemic: prevention education, risk assessment, early detection, follow up care after testing, and clinical care after diagnosis. Prevention and risk assessment are routine tasks completed by most clinicians as they screen all patients for new or developing problems related to, among other things, sexual and drug use activities. Diagnosing HIV infection may necessitate or require consultation and additional resources in all but the most experienced HIV-care clinicians. All clinicians need a basic level of understanding about HIV infection in order to enhance clinical skills and to make informed decisions about care and referral. In primary care, knowing where to go and what to ask enhances the ability to manage HIV infection. The goal of this sourcebook is to provide that information.

Basic Overview

Pathophysiology of HIV Infection

HIV is an RNA virus that was discovered in 1983. HIV is a retrovirus. It replicates in a “backward” manner using a DNA template to replicate new RNA. Like all viruses, HIV is an obligate parasite: It cannot survive and replicate unless it is inside a living cell. HIV enters a cell when glycoprotein “knobs” on the viral envelope bind to specific CD4 receptor sites on the cell’s surface. Once bound, the virus is internalized and its genetic material is uncoated. In the cell, viral RNA is transcribed into a single strand of viral DNA with the assistance of an enzyme called reverse transcriptase. This strand replicates itself, becoming double stranded viral DNA. At this point, the viral DNA can enter the cell’s nucleus and insert itself into the host genome with the assistance of the enzyme integrase. Viral DNA in the genome then directs viral replication in the cell. The initial step in viral replication produces a long strand of viral RNA that must be cut to appropriate lengths. A viral enzyme called protease is required for this cutting process. New virions are then assimilated and bud out from the cell, taking a piece of the cell’s membrane to form the new viral envelope.

Although HIV can infect several types of human cells, immune dysfunction results predominantly from the destruction of helper T cells, more appropriately called CD4 + T lymphocytes (or CD4 + T cells) that play a pivotal role in the human immune response. These cells recognize infectious and neoplastic processes and then secrete cytokines that initiate the body’s defense mechanisms. CD4 + T cells are targeted by HIV because they have more CD4 receptor sites on their surfaces than other cells.

HIV produces immune deficiency by destroying CD4 + T cells. The number of CD4 + T cells is the primary marker for immune function in HIV and, as such, is the main determinant of risk for developing opportunistic disease. These diseases rarely occur early in the course of HIV disease when the CD4 + T cell count is near normal (800-1200 cells/mm³). As the disease progresses and the number of CD4 + T cells falls, the risk of opportunistic disease increases.

HIV is a dynamic disease, with billions of virions produced daily. Immediately after infection, the virus replicates rapidly, producing a high viral burden in peripheral blood during the first few weeks of infection. Initial infection is associated with a significant drop in CD4 + T cells and an increased viral load. An immune response is triggered, leading to rapid CD4 + T cell replacement and HIV-specific antibody production. The viral burden drops as the immune response is established. During initial infection, patients may experience fever, headache, diffuse lymphadenopathy, muscle and joint pain, diarrhea, sore throat, and/or rash. This mononucleosis-like illness usually occurs 2-12 weeks after exposure and symptoms can last two-to-three weeks or longer. Some patients also experience meningitis or encephalitis. The initial illness in HIV infection is called *acute or primary HIV infection or seroconversion illness* and if diagnosed, patient should be considered for acute treatment (see page 11).

In the absence of treatment, HIV infection will usually progress slowly in a fairly predictable pattern (Figure 1).

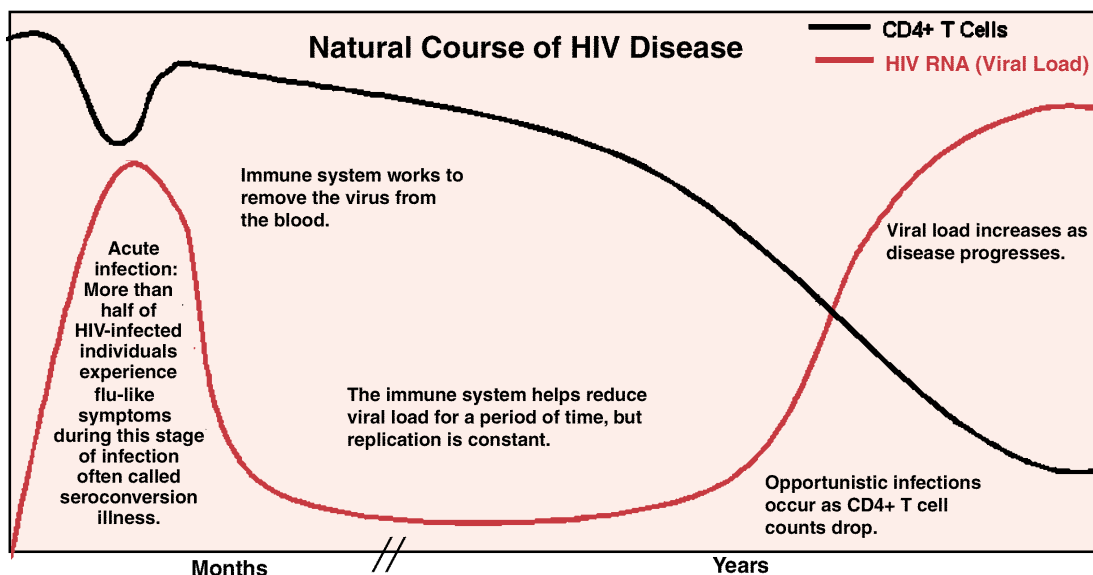


Figure 1. The natural progression of HIV disease. Without intervention, viral load will continue to increase as CD4 + T cell counts decline.

Table 2. List of Conditions in the 1993 AIDS Surveillance Case Definition

- CD4 + T-cell count of $< 200\text{mm}^3$ or $< 14\%$
- Candidiasis of esophagus, bronchi, trachea, or lungs
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month duration)
- Cytomegalovirus (CMV) disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- HIV encephalopathy
- Herpes simplex (HSV): chronic ulcers (> 1 month duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month duration)
- Kaposi's sarcoma (KS)
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary in brain (*AIDS with negative HIV-antibody test if patient < 60 yrs)
- *Mycobacterium avium* complex (MAC), or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* (MTB), any site (pulmonary or extrapulmonary)
- *Mycobacterium*, other species or unidentified species disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy (PML)
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

Clinical manifestations depend on the stage of infection, i.e. whether it is early infection with little immune dysfunction, or whether the infection has caused moderate or severe immune impairment. Different manifestations present at different stages of disease.

AIDS is a specific diagnosis that indicates progressive or advanced disease. The 1993 AIDS surveillance case definition includes all HIV-infected people with less than $200\text{ CD4+ T cells/mm}^3$, or a CD4 + T cell proportion (CD4 %) less than 14% of total lymphocytes or one of the AIDS-defining conditions listed in Table 2. An AIDS diagnosis does not always change clinical management but, in some cases, establishes eligibility for social services.

Risk Assessment and Harm Reduction

Identifying Risk

Healthcare providers have an important role to play in HIV prevention and early detection. Infected people can only be identified if the disease is first suspected. Considering the importance of counseling HIV-infected people about not spreading the disease

as well as the importance of early treatment, it is crucial that clinicians identify people at risk for HIV infection as early as possible. Risk is assessed by means of the medical and social history. Specific history items should relate to modes of transmission and risks associated with HIV infection, as noted in Tables 3 and 4.

Medical Conditions Associated with HIV Infection

HIV-infected patients can present at any point along the disease continuum. Signs and symptoms of HIV infection are frequently subtle and can be easily missed if an HIV diagnosis is not considered. For example, a young man with persistent cough and a menopausal woman with difficult to treat vaginal candidiasis may both be demonstrating immune suppression related to HIV. Early identification of HIV infection depends on the alert clinician. Some common

Table 3. Major HIV Transmission Mechanisms

- Contact with HIV-infected blood, semen, vaginal secretions, or breast milk
- Major means of transmission:
 - unprotected anal and/or vaginal intercourse
 - sharing used injection equipment
 - perinatal transmission

clinical conditions associated with HIV infection are included in Table 4. This list is by no means exhaustive, but if signs and symptoms are unusual or indicate immune suppression, the clinician should consider HIV in the differential diagnosis.

Risk Behaviors

Major behavior risks for HIV infection are related to unprotected sexual activities and sharing of injection equipment. Many patients and their clinicians find it difficult to talk about these private and sometimes stigmatized activities, but these discussions can form the basis of appropriate and comprehensive health care. Inquiring about sexual behavior and drug use should be included as part of every comprehensive risk assessment. In addition to discovering risk behaviors, the risk assessment can:

- Provide opportunities for knowledge assessment
- Determine the need for prevention education

Table 4. History Items to Assess Risk for HIV Infection

- unprotected sexual intercourse
- sexual contact with any person at risk
- multiple sex or drug-using partners
- injection drug use
- sharing injection equipment
- alcohol dependence or detoxification
- crack or cocaine use, even if not injected
- homelessness
- occupational exposure to human blood or body fluids and tissues
- children born to infected mothers
- transfusion or transplant
- hemophilia or coagulation disorders
- psychiatric hospitalization
- any other sexually transmitted disease (STD)
- abnormal PAP smear
- pelvic inflammatory disease (PID)
- pregnancy
- TB
- community-acquired pneumonia
- shingles (varicella zoster virus)
- recurrent vaginal candidiasis
- psoriasis or seborrheic dermatitis
- mononucleosis syndrome
- weight loss
- Bells palsy (sometimes associated with varicella zoster virus)
- Persistent generalized lymphadenopathy (PGL)

Table 5. Key Points for the Risk Assessment Interview

- Risk assessments should be done with every new patient and updated on a regular basis because circumstances and behaviors change.
- Sexual and drug using risks should be ascertained within the context of an overall risk assessment that includes questions about seat belt use and car safety, tobacco and alcohol use, domestic violence, and other health issues.
- Ask less threatening questions first:
 - "Have you ever had a transfusion?" before "Have you ever had a needle stick at work?"
 - "Are you sexually active?" before "Have you ever had anal intercourse?"
 - "Do you smoke cigarettes?" before "Have you ever injected drugs or other substances?"
 - For HIV risk, ask about blood contact (occupational, transfusion) before drug use and then discuss sexual issues.
- Start with a qualifier: "I am going to ask some personal questions. I ask these questions of all my patients because they help to determine appropriate care." or "Some medical conditions may be related to a person's behaviors. I will only ask questions about the things I need to know to help us work together to improve your health care."
- Respect a patient's choice to not answer a question. This increases the chance that s/he will provide the information at a later date.
- Labels can be misleading and may reveal personal prejudices.
 - Some men do not consider themselves "gay" if they practice anal insertive intercourse, but their receptive partners may be considered to be "gay."
 - The question, "Are you a homosexual?", may be answered negatively by a person who has had only a few same sex encounters or who considers him/herself to be bisexual.
 - Words like "junkie", "queer", and "hooker" are pejorative. They are not appropriate for clinical settings. Use other terms: "drug user", "men who have sex with men", "women who have sex with women", or "sex worker."
- It is best to ask direct questions about specific behaviors.
 - "Are you sexually active?" If the response is positive, follow with, "Do you have sex with men, women, or both?" "Do you have more than one sexual partner?" "Have you had sex with strangers?" "Do you use protection during sexual activity? How? When?" "What do you know about the sexual activities of your partner(s)?"
 - "Have you ever injected drugs or other substances?" If so, "Do you share your injecting equipment with anyone else?" "Do you clean your equipment between uses? How?" "Where do you get injecting equipment?"
 - "Do you have any tattoos?" If so, "When did you get it?" "Where did you get it (prison, tattoo parlor, foreign country)?"
 - "How many body piercings do you have?" "How was it pierced?" "Did you share piercing equipment?"
- Do not assume anything. Marriage does not guarantee that a person is monogamous or heterosexual. Being handicapped or elderly does not preclude sexual or drug using activity.
- Exploratory questions may help, especially with teenagers: "How easy is it to get drugs?" "Do your friends use condoms?" "What happens at parties?"
- Honest responses may be more forthcoming if the question is worded in such a way as to "normalize" the behavior: "Some people (inject drugs, have anal intercourse, exchange sex for drugs or money, etc.), have you ever done that?"

At the end of a risk history, summarize the patient's responses to be sure both the clinician and the patient understand what was said.

- Assist with testing decisions
- Open the door for further discussions

The value of risk assessment in the overall process of health care should not be underestimated. Table 5 provides key points in the risk assessment interview.

Reducing Risk

The purpose of a risk assessment is to discover behaviors that can be modified to improve patient health. Risk reduction counseling educates patients about ways to change risky behaviors. Harm Reduction is a philosophical base that acknowledges the challenges associated with behavior change and embraces pragmatic approaches to this sometimes difficult process. Harm reduction respects the value and dignity of humans through non-judgmental, supportive, and individually-focused interventions that allow patients to make their own decisions. The central concept of harm reduction is that any

movement toward healthier, safer, or less risky behavior is positive even if absolute protection is not attained. A harm reduction approach maintains that behavior change is best accomplished through a series of small, personally acceptable, and attainable steps. Clinicians begin to implement harm reduction by helping patients assess and acknowledge personal risk. When risk is identified, the patient is asked: “What would be safer, healthier, or less risky than your current behavior(s)?” Responses are then used to discuss those safer/healthier/less risky behaviors that are acceptable to the patient. This tactic provides a spectrum of choices while reaffirming the patient’s control over personal life events. Table 6 reviews sexual- and drug-related HIV prevention measures from a harm reduction perspective, creating a continuum from SAFE (behaviors that eliminate risk) to RISK REDUCING (behaviors that decrease risk, but do not eliminate it) to HIGH RISK (behaviors that place the individual at added risk of infection).

Table 6. Harm Reduction for Prevention of HIV Infection

	Sexual Transmission	Drug Use	Perinatal Transmission
SAFE BEHAVIORS (no risk of HIV transmission)	<p>Not having sex.</p> <p>Limiting sex to activities in which the penis, vagina, mouth, and/or rectum have no contact with the partner’s penis, vagina, mouth, and/or rectum (outer-course).</p> <p>Having sex only in a mutually monogamous relationship with an uninfected partner.</p>	<p>Not using drugs.</p> <p>Not injecting drugs: if drugs are used, smoke, snort, swallow, or apply to oral or rectal mucosa instead.</p> <p>If injection is required, using only clean equipment that has not been used by anyone else.</p>	<p>Preventing HIV infection in women.</p> <p>In HIV-infected women:</p> <ul style="list-style-type: none"> • Using birth control to prevent pregnancy. • Terminating the pregnancy. (No woman with HIV should be forced to have an abortion, nor should she be refused one if that is her choice.)
RISK REDUCING BEHAVIORS (decrease but do not eliminate risk)	<p>Using barriers consistently and correctly:</p> <ul style="list-style-type: none"> • Oral intercourse on male: Use non-lubricated male condoms. • Oral intercourse on female: use dental dams, plastic wrap, or latex panties. • Vaginal intercourse: use male or female condoms. • Anal intercourse: use male condoms or female condoms with inner ring removed. 	<p>Cleaning used injecting equipment before use:</p> <ul style="list-style-type: none"> • Rinse used needle and syringe with tap water. • Fill used syringe and needle with full-strength household bleach, shake for 30 seconds, squirt bleach out; repeat these steps twice. • Rinse by filling syringe with tap water and squirting water out; repeat this step twice. • Do not reuse or share bleach or rinse water. 	<p>Planning pregnancy early at a time when mother’s viral load is low and the CD4 + T cell count is relatively high.</p> <p>Treating infected mother with appropriate ART during pregnancy and IV zidovudine (AZT, ZDV, Retrovir®) during labor and delivery; considering elective Cesarean section; treating newborn with ZDV for six weeks after birth. (See treatment guidelines for pregnancy.)</p>
HIGH RISK BEHAVIORS (no protection from HIV or other diseases)	<p>Having unprotected insertive sexual intercourse.*</p> <p>Having unprotected anal intercourse.*</p> <p>*The receptive partner in insertive sexual intercourse is at higher risk than the insertive partner.</p>	<p>Sharing used injection equipment</p> <p>Having unsafe sex while under the influence of any drug, including alcohol.</p>	<p>Becoming pregnant during later stages of mother’s infection when immune system is more likely to be compromised and viral burden is higher.</p>

Adapted from: Bradley-Springer, L. (1999). *HIV/AIDS Nursing Care Plans*, 2nd edition. El Paso, TX: Skidmore-Roth Publishing.

Diagnosing HIV Infection

Provide education and referrals specific to the patient's chosen harm reducing behaviors. Let the patient take the lead on this. It does little good to discuss abstinence, for instance, if the patient has said she'd like to try to use female condoms. When a patient chooses abstinence, it is important to discuss refusal skills rather than having a condom demonstration. And, because transmission from HIV-infected drug users to their sexual partners is a common route of infection, all counseling to drug users should include information about safer sex.

Occupational Exposure to HIV

The risk of exposure to blood and blood borne pathogens is slightly greater for health care personnel (HCP) than for people who don't work around blood. An exposure that would create such a risk is defined as a percutaneous injury (needle stick or cut with a sharp object) or mucous membrane or non-intact skin contact where the exposure is to infected blood, tissue, or other body fluids. The risk of infection from an occupational exposure to HIV is small. A percutaneous exposure to HIV-infected blood results in infection approximately 0.3% of the time; other types of exposures (to intact skin, etc.) are considerably lower. CDC and Occupational Safety and Health Administration (OSHA) policies require employee protection from exposure to infectious fluids in the work setting. Practicing Standard Precautions (including Body Substance Isolation) and the use of Personal Protective Equipment (PPE) such as gloves, gowns, boots, eyewear, and masks as appropriate for patient care decreases the risk of direct contact with blood and body fluids, thereby decreasing the risk of infection with all blood-borne pathogens.

Currently, the CDC recommends postexposure prophylaxis (PEP) based on the nature and severity of the exposure, the exposure severity, and the broader range of antiretroviral drugs available. The availability of treatment makes the reporting of all blood exposures extremely critical. It also increases the need for clinicians to know PEP treatment basics and to seek expert consultation.

For further information regarding occupational exposure and PEP, refer to appendix A.

People who are identified as being at risk for HIV should receive pre-test counseling and encouragement to be tested. Pre-test counseling guidelines are available from a variety of sources. Basically, pretest counseling consists of a process starting (as previously discussed) with a risk history and an explanation of prevention measures. Information about the test, what the test can and cannot determine is also necessary. Most states require informed consent prior to testing because of the emotional, physical, and social implications of having a diagnosis of HIV infection. HIV infection is a reportable disease in most states, while AIDS is reportable in every state.

Table 7. Window Period for HIV Testing

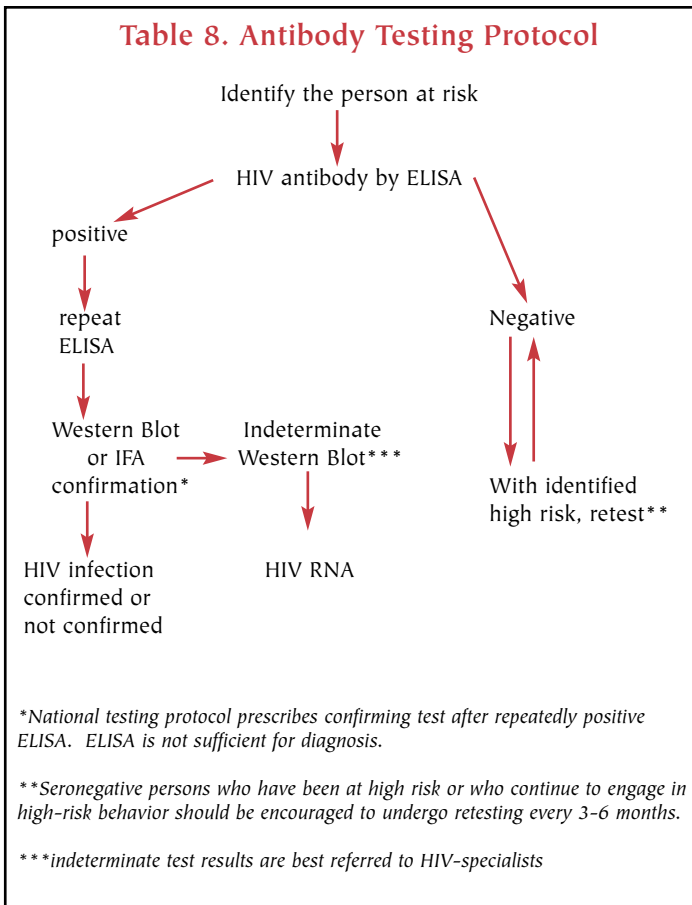
The window period is the time between infection with HIV and producing enough HIV antibody to be detected through testing.

- The EIA or ELISA screens for antibodies to HIV, not for the virus itself.
- In general, 3-12 weeks after infection is required to produce enough antibody to register a positive EIA or ELISA. In rare cases, it may take as long as 6 months for an HIV-infected person to produce a positive EIA or ELISA test result. A recently infected person can infect others even while testing antibody negative.
- A recently exposed person should be advised to return for HIV antibody testing 6 weeks and 3 months after exposure. This assumes that no other HIV risk behaviors or potential exposures occur in the meantime.
- Appropriate recommendations for further testing and risk prevention depend on an understanding of the window period.
- Persons concerned about a potential exposure should take precautions to decrease the risk of HIV transmission to others during the window period.

The usual test for antibodies to HIV, the enzyme-linked immunoassay (EIA or ELISA), is a highly sensitive, low-cost test that is well suited to screen for HIV. Patients need to understand the test detects antibody rather than actual virus and may, therefore, not detect a recent infection (Table 7). ***During this "window period," a negative test does not rule out HIV infection.*** A negative test in a person with recent or continuing risks should, therefore, be followed by a repeat test in a few weeks to months.

A repeatedly positive test must be confirmed by a more specific test, such as the Western Blot or immunofluorescent assay (IFA) before concluding that a

Table 8. Antibody Testing Protocol



individual. High-risk behavior anytime during the previous six months indicates the need for another HIV test in six weeks to three months. Reinforcing risk reduction behaviors is also appropriate.

A positive test result is more difficult to disclose and clinicians should be prepared for an emotional response from the patient. Some patients become understandably distressed about a positive test and it is appropriate to assess support systems (e.g. friends, family, mental health counselor), determine suicide risk, and make referrals as needed. Post-test counseling should be individualized to the patient, but needs to include the following:

- Remind the patient that HIV infection is treatable and that many people remain well for prolonged periods.
- Convey that there is a responsibility to avoid spreading the disease to others.
- Review safer sexual and drug use practices.
- Patients should encourage their high-risk contacts to be tested. State health departments are equipped with specific guidelines for notifying high-risk contacts about the need for testing.
- Assure patient understanding of the need for care and set up a return appointment within the next one-to-three weeks.

Treatment

Treatment options for HIV disease have advanced rapidly since 1995, primarily due to the development of new antiretroviral agents and the recognition that combination antiretroviral therapy (ART) is far better than less aggressive treatment strategies at inhibiting viral replication, preventing drug resistance, and preventing immune dysfunction. With a comprehensive treatment plan, people with HIV infection can live for many years.

Clinical Assessment

An individualized treatment plan for a patient with HIV infection is based on medical history, physical exam, and laboratory analysis. These provide baseline assessments and information about treatment options.

Medical History In addition to obtaining a history of risk factors (as previously discussed), a basic medical history to elicit symptoms of early HIV infection is essential. Table 9 lists some important questions to ask HIV-infected people during the medical history.

person is actually infected with HIV. The algorithm for HIV testing is given in Table 8. The Western Blot test result may be indeterminate, creating uncertainties about whether HIV infection is present or not. In this instance, the clinician should seek consultation from a reference laboratory or HIV specialist; the patient should be counseled about the uncertainty of the result and the need to continue precautions to prevent sexual or drug use transmission.

Post-test counseling is conducted when test results are available. Test results should be revealed in a face-to-face and private setting. Negative test results should be discussed in terms of the risk for a false negative result based on the window period and assessed risk for the

Doctor Ordered to Pay Over HIV Test

A judge in Australia found a doctor guilty of negligence for not recommending that a heterosexual male patient with hepatitis B and a history of recurrent viral illnesses be tested for HIV. A woman who contracted HIV in 1993 from the patient was awarded \$703,414 plus medication costs and interest. The judge noted that while the physician could not force the man to be tested, the patient would have been tested if the physician had provided appropriate counseling.

- Australian Associated Press (11/05/99)

Table 9. Initial History Pertinent to HIV Infection

- History of previous HIV testing and test results?
- Past exposure to related infections?
 - hepatitis
 - other sexually transmitted infections
 - TB
 - any other potentially chronic infections, e.g. histoplasmosis, coccidioidomycosis
- Current signs & symptoms? Particularly:
 - weight loss, fevers, chills, night sweats
 - changes in mentation
 - headaches
 - changes in vision
 - pain in mouth, pharynx
 - difficulty swallowing
 - shortness of breath, cough, chest discomfort
 - diarrhea, nausea, vomiting
 - numbness, tingling, weakness in extremities
 - changes in skin
 - recurrent vaginal yeast infections

Table 10. Physical Examination of the HIV-infected Person

System	Physical Signs	Potential Etiology
General	weight loss, cachexia, fever, chills, fatigue, night sweats	HIV infection, opportunistic infection or malignancy
Skin	pigmented lesions of recent onset, ulceration, erythema, exfoliation	Kaposi's sarcoma, herpes simplex or zoster, impetigo, seborrhea, folliculitis, xeroderma
Oral Mucosa	whitish plaques, ulceration, poor dentition, pigmented lesions	Candida, herpes, Kaposi's sarcoma, oral hairy leukoplakia, gingivitis
Eyes	diminished peripheral vision, funduscopic abnormalities, retinitis, change in acuity	CMV or HSV/VZV retinal necrosis
Chest	cough, fine rales, tachypnea, hypoxemia, pneumonia	PCP, CMV, pulmonary Kaposi's sarcoma, fungal pneumonia, tuberculosis
Anogenital	ulceration, fissures, discharge	herpes, STDs, pre-malignant HPV
Nodes	enlargement, especially noninguinal	MAC, lymphoma, TB, PGL
CNS	dementia, focal deficits, meningitis	HIV, PML, toxoplasmosis, lymphoma, cryptococcus

Physical Examination A complete physical examination is required for all patients with established HIV infection, even if no symptoms are present. Immune deficiency may allow infections to become established without early symptoms. Patients may not notice skin lesions, such as those found in Kaposi's sarcoma, especially if the lesions are in areas that are difficult to see. Careful inspection of the oral cavity and lymph nodes is especially important. Table 10 lists important physical findings in the HIV-infected patient, along with their major causes.

Laboratory Tests Of the many laboratory tests used to support diagnosis and therapy in HIV infection (see Table 11), two are critical: viral load assays and CD4 + T cell counts. The combination of viral load and CD4 + T cell testing provides the best information for initiating, monitoring, and changing ART. Viral load indicates the current level of virus circulating in the blood and the ability of the virus to multiply. CD4 cell

count measures the current ability of the immune system to protect the body.

For both tests, it is important to use the same laboratory test over time, to draw blood at the same time of day, if possible, and to avoid testing on days when the patient is acutely ill. HIV RNA testing should generally be avoided if the patient has been vaccinated or has had an acute infection within the preceding four weeks.

Table 11. Initial Laboratory Evaluation of the HIV-infected Person

The Basics

- CBC with differential
- Platelet count
- Chemistry profile (with LFTs)
- Baseline chest x-ray
- PPD test
- Cervical Pap smear
- Lipid profiles

Serologic Studies

- Syphilis serology
- Consider CMV serology
- HBsAb, HBcAb, HBsAg
- Toxoplasmosis serology
- Hepatitis C serology

HIV-Specific Tests

- CD4 + T cell count (absolute and percentage)
- Viral load by branched DNA (bDNA), PCR, or other assay

Viral Load Testing (HIV RNA Assay). Viral replication in HIV infection is rapid and continuous. From the time of infection billions of new viral copies are produced daily. Viral load is a quantitative measure of HIV viral RNA in the plasma. A stable level or "set point" occurs after primary infection and remains relatively constant in the absence of disease progression, therapeutic effect, or disease exacerbations. Plasma HIV RNA quantitation is the best determinant of treatment efficacy.

Three commercially available assays can determine viral load: branched chain DNA (bDNA), quantitative polymerase chain reaction (RT-PCR), and nucleic acid sequence-based amplification (NASBA). While correlation between plasma HIV RNA levels is high between methods, each is a distinct technique with different reference standards. Each technique has a different definition of “undetectable,” none of which indicate a total absence or clearance of virus. See Table 12 for further information on viral load testing. It should be noted that HIV viral load testing has been approved by the FDA for determining prognosis and for monitoring the response to therapy only for the RT-PCR assay (Roche).

CD4 + T Cell Count. The CD4 + T cell count is the best marker for immune deficiency associated with HIV infection. The CD4 + T lymphocyte count reflects the number of CD4 + T cells/mm³ circulating in the blood. The laboratory will sometimes report a list of several types of lymphocytes, with relative percentages, as well as absolute count. The important numbers are the absolute number of CD4 + T cells/mm³ and the proportion of CD4 + T cells as a subset of all lymphocytes (CD4%). Depending on the laboratory, the normal range for an adult CD4 + T count will be about 800-1200 cells/mm³ with a percent (of total lymphocytes) of more than 20-25%. The absolute CD4 + T count can vary in the same individual depending on what time of day the blood is drawn, the laboratory used, the presence of acute illness, or other factors such as alcohol binging.

HIV Resistance Testing. Resistance to antiretroviral medications is a major clinical concern: resistance leads to treatment failure and the risk of transmitting HIV that is resistant to the currently used antiretroviral medications. Two types of laboratory assays are currently available to help determine resistance: phenotypic resistance testing, which determines if the patient’s HIV can grow in the presence of specific antiretroviral agents (similar to antibiotic sensitivity testing) and genotypic resistance testing, which looks for mutations in the genetic code of the HIV that are associated with drug resistance. Although resistance testing has a number of clinical applications (from determining whether the patient was infected with a drug-resistant strain of HIV to prescribing effective

Clinical Indication	Information	Use
Syndrome consistent with acute HIV infection	Establishes diagnosis when HIV antibody test is negative or indeterminate	Diagnosis
Initial evaluation of new HIV diagnosis	Baseline viral “set point”	Decision to start or defer therapy
Every 3-4 months in patients not on therapy	Changes in viral load	
4-8 weeks after initiation of ART	Initial assessment of drug efficacy	Decision to continue or change therapy
3-4 months after start of therapy	Maximal effect of therapy	
Every 2-4 months in patients on therapy	Durability of antiretroviral effect	
Clinical event or significant decline in CD4 + T cells	Association with changing or stable viral load	

medications), both types of testing are expensive; results take two-to-four weeks and are sometimes difficult to interpret. Performance and interpretation of these tests should be done in collaboration with an HIV expert.

Additional Laboratory Evaluation. Additional laboratory evaluation should include tests to identify HIV-related complications or co-infections (syphilis serology, tuberculin skin test, gynecologic exam with Pap smear, hepatitis C virus [HCV] serology, and toxoplasma IgG serology) and tests to establish baseline metabolic parameters (serum glucose, triglyceride, and cholesterol). Other tests should be performed as clinically indicated (e.g., chest X-ray and ophthalmologic exam). Hepatitis B virus (HBV) serology is indicated in a patient who is a candidate for the HBV vaccine, who has abnormal liver function tests, or who has a history of possible exposure. CMV serology may be useful in certain individuals (see bibliography for reference to *USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with the Human Immunodeficiency Virus*).

Table 13. Risks and Benefits of Delayed Initiation of Therapy and of Early Therapy in the Asymptomatic HIV-Infected Patient

	Potential Benefits	Potential Risks
Delayed Therapy*	<ul style="list-style-type: none"> • Avoid negative side effects on quality of life (i.e., inconvenience) • Avoid drug-related adverse events • Delay in development of drug resistance • Preserve maximum number of available and future drug options when HIV disease risk is highest 	<ul style="list-style-type: none"> • Possible risk of irreversible immune system depletion • Possible greater difficulty in suppressing viral replication • Possible increased risk of HIV transmission
Early Therapy*	<ul style="list-style-type: none"> • Control of viral replication easier to achieve and maintain • Delay or prevention of immune system compromise • Lower risk of resistance with complete viral suppression • Possible decreased risk of HIV transmission** 	<ul style="list-style-type: none"> • Drug-related reduction in quality of life • Greater cumulative drug-related adverse events • Earlier development of drug resistance, if viral suppression is suboptimal • Limitation of future antiretroviral treatment options

*See Table 14 for consensus recommendations regarding when to initiate therapy.

**The risk of viral transmission still exists; antiretroviral therapy cannot substitute for primary HIV prevention measures (e.g., use of condoms and safer sex practices).

Adapted from *The Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*; Department of Health and Human Services

Antiretroviral Therapy (ART)

Antiretroviral therapy has been demonstrated to slow disease progression and to improve survival and quality of life for HIV-infected patients. The goal of ART is to decrease or stop viral replication for as long as possible, thus reducing the chance of viral mutations and drug resistance. Combination drug regimens have proven effective in dramatically reducing the quantity of circulating virus in the blood, often to levels below detection. It is important to note, however, that not all patients can tolerate or adhere to combination therapy and 30-50% or more of patients fail to achieve the goal of undetectable virus.

It is also important to remember that an undetectable viral load does not mean the virus is gone or the patient is cured. “Below the level of detection” indicates the viral load in a peripheral blood sample is too low to be detected with current tests and does not

reveal the level of HIV that remains in the tissues. The long-term effects of the new treatments will not be known for quite some time. The initiation of ART should be based on the patient’s clinical presentation, disease progression, treatment history, desire for ART, and understanding of adherence parameters. See Table 13 for a discussion of the benefits and risks of early initiation of ART.

Antiretroviral Treatment Recommendations

With the advent of combination drug treatment regimens, ART has become quite complex. In May 1999, a panel of experts published revised principles and recommendations for HIV treatment. *The Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (see bibliography) recommend that clinicians with limited HIV-care experience seek the consultation of clinicians with experience in this complex and rapidly evolving field. Most primary care clinicians are familiar with utilizing consultative services for complex disease processes and this is a critical component of HIV care.

Key issues in the use of ART are summarized below. These are merely highlights — the complete principles and guidelines are available from the AIDS Education and Training Centers, the National AIDS Clearinghouse, or the HIV/AIDS Treatment Information Service (see bibliography and resources section).

Starting ART

Starting or changing therapy should be based on clinical status, viral load tests, and CD4 + T cell counts. Ideally, two sets of tests are obtained before making final treatment decisions. It is also important to assess whether the patient had an acute infection, illness, vaccination, or TB skin test within four weeks of the tests. Viral load tests should be conducted after the first four weeks of therapy and every three-to-four months thereafter in stable patients.

Table 14. Indications to Initiate Antiretroviral Therapy

Clinical Category	CD4 + Cell Count	Plasma HIV RNA	Recommendations
Symptomatic (AIDS, severe symptoms)	Any value	Any value	Treat
Asymptomatic, AIDS	< 200/mm ³	Any value	Treat
Asymptomatic	200 -350/mm ³	Any value	Treatment should generally be offered, though controversy exists. *
	> 350/mm ³	> 55,000 (by bDNA or RT-PCR)**	Some experts would recommend initiating therapy, recognizing that the 3-year risk of developing AIDS in untreated patients is > 30% and some would defer therapy and monitor CD4 + T cell counts more frequently.
	> 350/mm ³	< 55,000 (by bDNA or RT-PCR)**	Many experts would defer therapy and observe, recognizing that the 3-year risk of developing AIDS in untreated patients is < 15%.

DHHS Guidelines

*Clinical benefit has been demonstrated in controlled trials only for patients with a CD4 + T cells <200/mm³. However, most experts would offer therapy at a CD4 + T cell threshold < 350/mm³. A recent evaluation of data from the MACS cohort of 231 individuals with CD4 + T cell counts > 200 and < 350 cells/mm³ demonstrated that of 40 (17%) individuals with plasma HIV RNA < 10,000 copies/mL, none progressed to AIDS by 3 years (Alvaro Munoz, personal communication). Of 28 individuals (29%) with plasma viremia of 10,000-20,000 copies/mL, 4% and 11% progressed to AIDS at 2 and 3 years respectively. Plasma HIV RNA was calculated as RT-PCR values from measured bDNA values.

**Although there was a 2-2.5 fold difference between RT-PCR and the first bDNA assay (version 2.0), with the current bDNA assay (version 3.0), values obtained by bDNA and RT-PCR are similar except at the lower end of the linear range (< 1,500 copies/mL).

At the present time, most individuals with HIV infection are candidates for treatment. An exception to this may be the patient with a nearly normal immune system (as indicated by CD4 + T cell counts over 350 cells/mm³) and a low viral load (< 55,000 copies/mL by RT-PCR or DNA methodology), as defined by current guidelines. Guidelines suggest indications for ART as shown in Table 14.

Individual judgment and preference allow for reasonable practice differences, i.e., some experts may elect to observe rather than treat a patient with a high CD4 + T cell count and a low viral load, others choose to offer therapy to patients with detectable virus at any level. Decisions regarding the initiation of ART must be individualized to the patient after appropriate patient education regarding disease stage, drug side effects, long-term toxicity, co-morbidities, and adherence issues.

Treating Patients with Acute HIV Infection

Acute HIV infection (also called retroviral syndrome or primary HIV infection) occurs in 50-90% of HIV-infected people during the initial weeks of infection. HIV RNA levels are high during this period and then generally decline to a more stable level (the “set point”). Both clinician and patient should be fully aware that therapy for primary HIV infection is based on theoretical benefits, so the potential benefits and risks of treatment should be discussed (Table 13).

Although clinical trials information is limited in this area, most experts endorse treatment with combination therapy for acute HIV infection based on the theoretical rationale that treatment will:

- reduce viral replication and dissemination
- reduce symptoms of acute HIV infection
- alter the viral “set point”
- reduce the appearance of viral mutations

Consultation with an HIV-experienced clinician is recommended.

Medication Adherence

Adherence to treatment regimens is a critical therapeutic issue. Incomplete adherence can lead to treatment failure, drug resistance, and the risk for transmission of drug-resistant virus, making this a critical issue for patient education. Patient acceptance is a key to medication adherence, and it is important to allow the patient time to make the decision to initiate therapy. Further education and “trial runs” (i.e. providing a placebo course of medications) can help patients determine their abilities to adhere to the sometimes difficult treatment regimens.

Medication adherence can be a challenge for even the most motivated patients. While 100% adherence is optimal, missed dosages should be an expected part of treatment. Clinical studies indicate that best results are achieved with adherence rates of > 95%, a feat that is rarely achieved in other types of medication administration. HIV-infected patients who choose to initiate ART will need continuous support to maintain therapy. Judgmental and punitive approaches to less-than-optimal adherence should be avoided, as they are likely to decrease the patient’s willingness to share accurate information with the clinician. Table 15 lists some factors to consider when addressing adherence concerns with a patient. Adherence interventions should be individualized and consistent with the current treatment guidelines.

Currently Available Antiretroviral Drugs

Eighteen antiretroviral agents are now approved for use in the United States, but a number are awaiting approval and more are in development. Antiretroviral drugs fall into four classes: nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) (see Appendix B).

Nucleoside Reverse Transcriptase Inhibitors (NRTI) work at an early stage in viral replication. They block reverse transcriptase, an enzyme required for viral replication, by mimicking nucleosides in the growing DNA chain. This stops viral growth. NRTIs are the cornerstone of combination therapy.

The only **Nucleotide Reverse Transcriptase Inhibitor (tenofovir)** stops HIV from multiplying by blocking reverse transcriptase activity. This results in DNA chain termination. Once the DNA chain is terminated, the individual virus can no longer replicate. As viral replication decreases, damage to the immune system is slowed.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) also blocks reverse transcriptase action. Resistance develops quickly to NNRTIs when used alone, so it is important that they be used in maximally suppressive combination therapies. NNRTIs are often used in combination with NRTIs as “protease sparing” therapies. This tactic decreases exposure to PI-associated side effects and drug interactions while preventing resistance development to the PIs, a powerful group of agents that may be needed at a later date in the patient’s therapy.

Table 15. Medication Adherence

Factors that increase adherence:

- patient and provider rapport
- patient’s trust of provider and willingness to honestly disclose adherence problems
- fewer medications/fewer dosages per day
- patient’s belief in and personal experience of treatment efficacy
- effective reminder systems individualized to the patient
- frequent adherence review to identify problems and initiate problem solving
- ability to take medications in private, unobserved settings

Factors that decrease adherence:

- active dependence on substances such as drugs and alcohol
- undesirable or intolerable side effects
- lack of understanding about medications, side effects, treatment regimens, and support systems
- interactions with food or other medications

Protease Inhibitors (PI) work against HIV in a late stage of the viral replication process by interfering with the protease enzyme’s role in making new copies of HIV inside infected cells, thus producing viruses that are incapable of infecting new cells. The PIs, when used in combination with other antiretroviral agents, offer potent anti-HIV activity.

Other Antiretroviral Therapies. The list of antiretroviral therapies continues to grow as ongoing experimental trials provide new options for treatment. Information on HIV/AIDS experimental treatments and trials can be obtained from resources listed in the back of this sourcebook.

Antiretroviral Treatment Regimens

Combination therapy with at least three antiretroviral drugs is currently recommended for patients starting treatment. The complex decision of when and how to prescribe and enhance adherence to the regimens is left to the judgment of the clinician and the patient.

Not all patients can tolerate, adhere to, or achieve an undetectable viral load with combination therapy. Partial viral suppression, i.e. more than a one-half log reduction in viral load, has been shown to provide clinical benefit, although partial suppression supports the development of the drug resistance that can ultimately lead to treatment

Table 16. Recommended Antiretroviral Regimens for Initial Treatment of Established HIV

This table provides a guide to the use of available therapies for individuals with no prior or limited experience on HIV therapy. In accordance with the established goals of HIV treatment, priority is given to regimens in which clinical trials data suggest sustained suppression of HIV plasma RNA, sustained increase in CD4 + T cell count, and favorable clinical outcome (i.e. delayed progression to AIDS and death). Additional consideration is given to a comparison of regimen pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interaction profile. It is important to note that all antiretroviral agents, including those “Strongly Recommended”, have potentially serious toxic and adverse events associated with their use. *Physicians less experienced in HIV care are strongly encouraged to consult with specialists in HIV care, especially when initiating or adjusting ART regimens.*

Antiretroviral regimens are comprised of one choice each from columns A and B in the preferred category. Drugs are listed in alphabetical, not priority, order.

Recommendation Level:	Column A	Column B
Strongly Recommended	EFV IDV NFV RTV + IDV ^{1,2} LPV + RTV ^{1,3} RTV + SQV ¹	d4T/3TC AZT/ddI AZT/3TC d4T/ddI ⁴ ddI/3TC
Alternative	ABC APV DLV NVP RTV SQV (Fortovase) NFV/SQV (Fortovase)	AZT/ddC
No Recommendation (combinations for which information is too limited to recommend for or against use)	Hydroxyurea in combination with other antiretroviral drugs Ritonavir + Amprenavir ¹ Ritonavir + Nelfinavir ¹ Tenofovir ⁵	
Not recommended; should not be offered	Any monotherapy ⁶ SQV (Invirase) ⁷ ddC/ddI	ddC/d4T ddC/3TC AZT/d4T

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¹ Agents may be used at lower doses when combined with ritonavir. See consultation of an HIV expert and the guidelines for further information.

² Based on expert opinion.

³ Co-formulated as Kaletra.

⁴ The combination of ddI/d4T should be avoided in pregnant women due to the risks for lactic acidosis and hepatotoxicity.

⁵ Data from clinical trials are limited to use in salvage. Data from trials of Tenofovir as initial therapy may be available in the near future.

⁶ Zidovudine monotherapy may be considered for prophylactic use in pregnant women with low viral load and high CD4 + T cell counts to prevent perinatal transmission.

⁷ Use of Saquinavir (Invirase) is not recommended, except in combination with ritonavir.

failure and disease progression. Because of this, monotherapy and dual therapy are generally not recommended. Factors that contribute to resistance include inappropriate prescriptions, previous exposure to ART agents (especially in incompletely suppressive regimens), late stage disease with high viral loads and different viral strains, and patient non-adherence to treatment protocols. Specific recommendations on drugs to use and those to avoid in combination are shown in Appendix B.

Drug interactions can occur between some of the antiretroviral agents, especially the PIs and NNRTIs, and with other medications. Assessments for toxicities should be ongoing. See the Guidelines and/or consult a specialist for details on drug interactions.

Continuing Therapy

Response to therapy should be assessed four-to-six weeks after initiation of therapy with measurement of the CD4 + T cell count and viral load analysis. Adjustments should be made if the viral load does not decrease by at least 0.5 log during that time period. Fully successful regimens should reduce HIV levels to undetectable within four-to-six months.

Over the course of treatment, some patients with an initial good response to therapy will begin to show

decreases in CD4 + T cell counts and increases in viral loads, indicating a failure of the therapeutic regimen. Discussions with the patient should include an honest appraisal of adherence to the medication regimen and new treatment options. Changing therapy can be a complex process, but general recommendations are presented in Table 17.

Clinicians are urged to be conservative and take the time needed to make well-informed decisions with their patients. Consult HIV-experienced clinicians and the Guidelines for lists of potential alternative regimens, and be aware of the need to change at least two drugs in a failing regimen because changing only one can lead to resistance. Because all current PIs exhibit some cross-resistance, novel combinations are included in the Guidelines for the treatment of PI-experienced patients.

Recommendations regarding the meaning or the clinical utility of assays to measure genotypic or phenotypic resistance to antiviral therapies are in development. Viral load assessments can be used as indirect measures of drug failure from resistance or from other causes, such as inadequate absorption (e.g., due to vomiting or diarrhea), adverse drug interactions, or patient nonadherence to the drug regimen. It is important that critical treatment decisions such as regimen changes should only be made with the assistance of an HIV specialist.

Table 17. Guidelines for Changing an Antiretroviral Regimen for Suspected Drug Failure

- Criteria for changing therapy:
 - suboptimal reduction in plasma viremia after initiation of therapy
 - re-appearance of viremia after suppression to “undetectable”
 - significant increases in plasma viremia
 - declining CD4 + T cell count
 - clinical deterioration
- Confirm decision to change therapy with second viral load test.
- Distinguish between the need to change a regimen due to drug intolerance or inability to adhere vs. failure to sustain viral suppression.
- Do not change a single drug or add a single drug to a failing regimen, adjust at least two drugs at a time.
- Many patients have limited options for new regimens; in some of these cases it is rational to continue a prior regimen if partial viral suppression was achieved and if alternatives are limited.
- For patients with limited options (resistance or intolerance), combinations of four or more medications including the use of two PIs are sometimes used.
- Cross-resistance may be seen with a number of drugs in the same class.
- Resistance testing may provide valuable information as new regimens are considered.

Physicians less experienced in HIV care are strongly encouraged to consult with specialists in HIV care, especially when initiating or adjusting ART regimens.

Symptom Evaluation in the HIV-infected Patient

Diagnosis and treatment of opportunistic conditions associated with HIV can be difficult. Common causes of symptoms seen in HIV-infected patients are listed in Table 18. Clinicians should develop and use consultation and referral systems with specialists in HIV care to improve diagnosis of HIV-related conditions and the quality and length of patient lives.

Pulmonary Manifestations

In general, any pulmonary symptom, even if mild, warrants evaluation. The CD4 + T cell count influences the extent of the evaluation. If the CD4 + T cell count is below 200 cells/mm³, the patient is at an increased risk for *Pneumocystis carinii* pneumonia (PCP), and this

disease should be assumed to be the cause of any new pulmonary symptoms until proven otherwise. If the CD4 + T cell count is between 200 and 500 cells/mm³, PCP is still possible, but less likely. Patients with CD4 + T cell counts above 500 cells/mm³ are much more likely to have one of the more usual causes of pulmonary symptoms, such as bacterial or viral infection. A chest x-ray is usually recommended to determine the presence of any infiltrate, but in a person with a low CD4 + T cell count, the x-ray appearance of PCP, tuberculosis, and most other infections may be highly atypical compared to expected appearance in an immune competent host. Consider as tentative any diagnosis that is not based upon a positive stain or culture of an adequate specimen. Also consider that more than one pathogen may coexist. Unfortunately, obtaining and interpreting specimens may be difficult. Induced sputum may yield a diagnosis of PCP. If unsuccessful, the best test for PCP is bronchoalveolar lavage (BAL) during bronchoscopy, with centrifugation and special staining (e.g. silver stain or PCP Direct Fluorescent Antibody [PCP DFA]). This may not be available in small communities and constitutes an appropriate reason for referral. Tuberculosis can be suspected on the basis of a sputum AFB stain. Other conditions (most notably KS) that involve the lung will generally have to be diagnosed by biopsy.

It is occasionally appropriate to treat patients empirically for suspected pulmonary conditions. For a person with a very low CD4 + T cell count and a severe lung disease, it is appropriate to begin empiric treatment for PCP while awaiting lab results or making referral arrangements. Clinicians should consider the possibility of acute bacterial pneumonia, which can be quite severe in advanced disease, and empiric treatment with conventional antibacterials is also often appropriate. In the rural setting when the patient is very ill and diagnostic procedures are not immediately available, it is appropriate to begin broad-spectrum empiric coverage for PCP and bacterial infection (and even fungal infection, if suspected) until a more definitive diagnosis can be established.

For moderate to severe PCP, use of adjunctive corticosteroids is recommended. A consensus panel has recommended that the criteria for steroid use be an arterial PO₂ of less than 70mm Hg on room air (at sea level) or an a-A gradient of greater than 35 mm Hg (at sea level). The recommended dose is 40 milligrams of prednisone twice daily for five days, followed by 40 milligrams daily for five days, followed by 20 milligrams daily for eleven days. Prednisone should be started no later than 72 hours after initiating specific antipneumocystis therapy.

Nervous System Presentations

Neurological Syndromes

It is estimated that 70% of HIV-infected people may develop varying degrees of neurologic disease, causing changes in affect, behavior, and

Table 18. Common Causes of Signs and Symptoms in HIV Infection

Cutaneous diseases

- Cutaneous mycoses (tinea)
- Varicella herpes zoster (VZV)
- Herpes simplex (HSV)
- Folliculitis
- Molluscum contagiosum
- Verruca/Condyloma
- Kaposi's sarcoma (KS)
- "itchy red bump" disease

Pulmonary diseases

- Pneumocystis carinii* pneumonia (PCP)
- Cytomegalovirus (CMV)
- Bacterial pneumonia
- Coccidioidomycosis
- Cryptococcal pneumonia
- Histoplasmosis
- Mycobacterium tuberculosis* (MTB)
- Kaposi's sarcoma (KS)
- Lymphoid interstitial pneumonitis (LIP) in children

Neurologic diseases

- HIV-associated dementia
- CMV encephalitis
- Toxoplasmosis
- Peripheral neuropathy
- Progressive multifocal leukoencephalopathy (PML)
- Primary CNS lymphoma
- Syphilis

Ocular disease

- Cytomegalovirus (CMV)
- Varicella zoster virus (VZV)
- Herpes simplex virus (HSV)

Diseases causing lymphadenopathy

- HIV
- Mycobacterium avium-complex* (MAC)
- Mycobacterium tuberculosis* (MTB)
- Disseminated cat scratch disease (Bartonella)

Diarrheal diseases

- Cytomegalovirus (CMV)
- Bacterial pathogens
- Mycobacterium avium-complex* (MAC)
- Cryptosporidium
- Isospora*
- Giardia*
- Strongyloides*
- Kaposi's sarcoma (KS)

General wasting diseases

- Mycobacterium avium-complex* (MAC)
- Cytomegalovirus (CMV)
- Mycobacterium tuberculosis* (MTB)
- Strongyloides*
- HIV

Esophageal diseases

- Candida albicans*
- Herpes simplex (HSV)

Oropharyngeal diseases

- Candida albicans*
- Herpes simplex (HSV)
- Oral hairy leukoplakia (OHL)
- Gingivitis
- Aphthous ulcers

Anal/perianal and genital diseases

- Herpes simplex (HSV)
- Syphilis
- Gonorrhea (GC)
- Condyloma acuminata*
- Candida albicans*
- Chlamydia
- Human Papilloma Virus (HPV)

cognition, particularly in late stages of HIV infection. Neurologic symptoms can, however, present early in the course of disease and are the chief presenting complaint in about 20% of HIV-infected individuals. Minor cognitive impairment occurs in 20-to-40% of HIV-infected asymptomatic patients; more severe impairment may be seen in people with AIDS-defining illness.

Table 19 outlines the major neurologic syndromes of organic etiology associated with HIV infection. Some patients who are past the earliest stages of disease will have measurable deficits in cognitive function on psychological tests, though this is often subclinical. Clinical dementia also occurs and may be rapidly

progressive. Successful treatment of HIV, in general, is the most effective treatment of HIV-associated cognitive deficits, dementia, and encephalopathy. Cytomegalovirus can also cause encephalitis. Differential diagnosis of these conditions is difficult. The coexistence of CMV retinitis may provide a clue, but not a definite diagnosis. Detection of CMV by PCR in spinal fluid can be helpful. Global CNS dysfunction can also be a manifestation of fungal meningitis, particularly coccidioidomycosis or cryptococcal meningitis. In addition, clinicians should always consider CNS dysfunction due to syphilis in the diagnostic process.

Evaluation of global CNS dysfunction should generally include a CT or MRI brain scan to look for

Table 19. Neuropsychiatric Syndromes

BRAIN		Causes of mental status change (other than HIV itself)	
HIV dementia - early		toxic-metabolic	
Complaints/symptoms		<ul style="list-style-type: none"> side effects to drug therapy hypoperfusion states: hypoxia, anemia 	<ul style="list-style-type: none"> electrolyte imbalance: hyponatremia, SIADH hypotension
<ul style="list-style-type: none"> memory loss impaired concentration comprehension difficulties conceptual confusion apathy depressed mood agitation psychotic features 	<ul style="list-style-type: none"> mild-moderate cerebellar dysfunction hyperreflexia motor weakness psychotic features unsteady gait tremor clumsiness 	tumor	
Signs/findings		<ul style="list-style-type: none"> lymphoma 	<ul style="list-style-type: none"> Kaposi's sarcoma (rare)
<ul style="list-style-type: none"> psychomotor slowing impairment of information processing visuospatial disorganization mild frontal lobe dysfunction dysgraphia 	<ul style="list-style-type: none"> memory dysfunction dysarthria/dysnomia mild-moderate cerebellar dysfunction hyperreflexia motor weakness 	opportunistic infections	
HIV dementia - late		<ul style="list-style-type: none"> toxoplasmosis Cytomegalovirus (CMV) <i>Cryptococcus</i> <i>Treponema pallidum</i> (syphilis) Papovavirus (PML) <i>Mycobacterium</i> 	<ul style="list-style-type: none"> <i>tuberculosis</i> (MTB) fungi Herpes simplex virus (HSV) Varicella zoster virus (VZV)
Complaints/symptoms		emotional	
<ul style="list-style-type: none"> global dysfunction mutism aphasia amnesic features frontal lobe 	<ul style="list-style-type: none"> disturbance dominant and non-dominant parietal lobe signs organic hallucinations 	<ul style="list-style-type: none"> depression 	<ul style="list-style-type: none"> anxiety
Signs/symptoms		SPINAL CORD - MYELOPATHY	
<ul style="list-style-type: none"> weakness spasticity dyskinesia Parkinsonism 	<ul style="list-style-type: none"> ataxia myoclonus incontinence seizures 	<ul style="list-style-type: none"> Increased incidence of concurrent encephalopathy spastic-ataxic gait hyperreflexia 	<ul style="list-style-type: none"> urinary and/or fecal incontinence hyporeflexia or areflexia cerebrospinal fluid pleocytosis
		PERIPHERAL NERVOUS SYSTEM	
		<ul style="list-style-type: none"> Chronic distal symmetric polyneuropathy <ul style="list-style-type: none"> painful dysesthesias, numbness, weakness, paresthesias autonomic dysfunction 	<ul style="list-style-type: none"> Chronic inflammatory demyelinating polyneuropathy <ul style="list-style-type: none"> weakness, sensory deficits mononeuritis multiplex, cranial nerve palsies hyporeflexia or areflexia cerebrospinal fluid pleocytosis

evidence of mass lesions or cortical atrophy, the latter of which is seen in HIV encephalopathy. A spinal tap is also appropriate, to include an analysis of CSF opening pressure, protein, glucose, and cell counts, as well as fungal and bacterial culture, cryptococcal antigen studies, AFB stain and culture if there is suspicion of tuberculosis, and syphilis serology. For global or focal CNS dysfunction, CMV PCR, VZV PCR, EBV PCR, and JC virus PCR on CSF may be helpful in determining etiologies.

Focal CNS findings suggest a mass lesion. Common causes in HIV-infected patients include CNS toxoplasmosis, primary CNS lymphoma, and PML. A presumptive diagnosis of CNS toxoplasmosis may be made by a positive serum toxo IgG serology plus the characteristic ring-enhancing lesion on CT. A brain biopsy is the definitive diagnostic procedure, but is not always necessary. CNS toxoplasmosis is difficult to treat, but may respond to a combination of pyrimethamine and sulfadiazine or pyrimethamine and clindamycin. CNS lymphoma lesions also ring-enhanced and can be treated with chemotherapy and/or radiation therapy, but the prognosis may be poor. If aggressive therapy of either of these conditions is appropriate for the patient, a referral should be considered. There is no effective therapy for PML, although improvement has been seen with aggressive ART.

Peripheral Nervous System

The most common peripheral nervous system complication of HIV disease is peripheral neuropathy. It is usually the result of drug therapy. The nucleoside analogues ddI, ddC, and d4T can cause painful peripheral neuropathy. Because neuropathy may also be the direct result of HIV, treating HIV with agents other than those known to cause neuropathy may be the best choice to resolve the neuropathy. If recognized early, discontinuation of ddI, ddC, and d4T may result in resolution of neuropathic symptoms.

Ocular Involvement

Cytomegalovirus (CMV) infection is the most common cause of retinitis and sight-threatening ocular disease associated with HIV, affecting 20-40% of infected people not receiving effective ART. Symptoms occur in late disease (CD4 + T cell count < 50 cells/mm³), generally presenting unilaterally but often

spreading to both eyes. CMV may initially be asymptomatic. Lesions may involve the peripheral retina, producing symptoms only when critical visual structures are affected or they may involve central retinal structures, in which case they may be immediately sight-threatening. CMV may be difficult to observe with a direct ophthalmoscope. Some clinicians screen patients for CMV retinitis through ophthalmologic referral for routine, biannual fundoscopic examinations when the patient's CD4 + T cell count is < 100 cells/mm³. CMV retinitis may be effectively treated with intravenous cidofovir, ganciclovir, valganciclovir; or foscarnet, or ganciclovir ocular implants in combination with oral or IV therapy. The majority of patients respond to one of these drugs. It is important to differentiate CMV from cotton wool spots (CWS), the most common ocular abnormality associated with HIV. CWS are asymptomatic and benign. Management of CMV retinitis is complex and warrants referral to an HIV-experienced ophthalmologist and clinician.

Cutaneous Manifestations

Recurrent herpes simplex (HSV) and varicella zoster (VZV) are frequent causes of morbidity in HIV infection. Because of impaired immune response, the appearance of these conditions may be unusual, sometimes forming superficial ulcerated areas without the typical vesicle formation. Confirmation of the diagnosis by culture should be done if available. Prolonged prophylaxis with acyclovir may prevent outbreaks, but lesions tend to recur when acyclovir is stopped. Ganciclovir treatment for CMV infection is also active against herpes.

Minor afflictions of the skin are commonly seen in people with HIV infection. Cutaneous mycoses (tinea) are diagnosed and treated in the usual way. Xerosis is managed symptomatically. Seborrheic dermatitis is very common in this population, especially on the face. Ketoconazole or itraconazole cream applied topically may be effective for chronic seborrheic dermatitis. Molluscum contagiosum and veruccae may be extensive and must generally be removed by excision or cryosurgery. It is common for people with HIV infection to have "itchy red bumps," and this condition has merited its own descriptive name in the

literature. This syndrome has several possible etiologies, including fungi and bacteria, and a skin biopsy and cultures may be necessary to establish the diagnosis if more than symptomatic therapy is desired.

Kaposi's sarcoma (KS) is the most common cutaneous malignancy in people with AIDS. It is seen almost exclusively in men who have sex with men. The appearance of purplish subcutaneous nodules is usually typical enough to permit a clinical diagnosis, but a biopsy is the definitive test if there is doubt about the nature of a lesion. It is now known that KS is caused by a viral infection with human herpes virus type 8 (HHV8). The cutaneous form is seldom fatal, but visceral involvement, particularly gastrointestinal or pulmonary, carries a poor prognosis. Cutaneous KS can be extensive and disfiguring, so patients will often desire treatment. Potent combination ART will often improve or resolve cutaneous KS with no further treatment. However, if further intervention is needed, several treatments are available, including radiation therapy, direct lesion injection with chemotherapeutic agents, and systemic chemotherapy. These are usually palliative and may improve the patient's quality of life. A decision to treat and selection of treatment modalities must be individualized with consideration of the patient's wishes and prognosis. If treatment is desired, a referral to an expert clinician will almost always be necessary.

Oral Health Care

Dental health care personnel (DHCP) play an important role in the comprehensive health care of HIV-infected patients and are essential members of the treatment team. Several conditions associated with HIV, including candidiasis, herpes, and Kaposi's sarcoma, can first appear inside the mouth. Because of this, DHCP may be the first to suspect HIV infection and are instrumental in providing appropriate referrals for HIV testing, counseling, and clinical care. Aggressive prophylactic oral care can reduce difficulties related to oral pathology, medical, nutritional, psychological, and social complications as well as improve immune function.

In HIV disease, oral health can decline as a result of systemic illness or when socioeconomic factors

prevent access to care. A combination of active oral disease and lack of dental care can cause debilitating oral pain, impaired nutrition, esthetic concerns, and the need for emergency treatment. Delays in oral health care can lead to tooth loss in immune compromised patients who will also be at risk for complications from invasive oral procedures. All of these may lead to negative repercussions on the patient's self-esteem, independence, or ability to work.

Advances in antiretroviral therapies that keep CD4 counts above 200 cells/mm³ and viral loads below 20,000 copies/mL have been associated with better oral health in HIV-infected patients. While this is encouraging, it does not decrease the need for proactive dental care for HIV-infected patients; routine prophylactic appointments and aggressive intervention for developing problems should continue.

Table 20 gives basic information on oral manifestations typically seen in HIV infection. As always, consultation and referral are appropriate when caring for HIV-infected clients with complex pathologies.

Metabolic Complications

Wasting Syndrome

The classic HIV-related wasting syndrome, manifested by loss of weight and lean body mass, has been seen less often in the United States since the widespread implementation of effective therapy for HIV infection, but can still occur, especially in those for whom treatment has failed. Weight loss is a multifactorial problem related to inadequate energy intake, metabolic dysregulation, side effects of medications, malabsorption syndrome, and/or infectious processes related to HIV and opportunistic disease.

Inadequate energy intake is associated with lesions in the mouth, pharynx, or esophagus due to infective processes such as *Candida*, CMV, or herpes virus; noninfective lesions, such as aphthous ulcers; poor oral hygiene; gastrointestinal disturbances due to medications; and psychosocioeconomic stressors, like bereavement, loneliness, depression, or concern about financial resources. Ongoing diarrhea is a major

Table 20. Common Oral Lesions in HIV

CLINICAL MANIFESTATIONS	CD4	DIAGNOSIS	TREATMENT OPTIONS
Candidiasis			
Pseudomembranous – local yellow-white plaque; surrounding mucosa may be red; most often seen on palate, tongue, buccal mucosa, and gingiva	typically present at CD4+ T cell counts of < 300 cells/mm ³	Frequently diagnosed by clinical appearance; easily confirmed by cytologic smear or culture	Topical: clotrimazole troches, nystatin oral suspension; Systemic: fluconazole, itraconazole, ketoconazole; Refractory disease: fluconazole, amphotericin, itraconazole
Erythematous, Atrophic – Localized or diffuse erythematous area (light to fiery red); most often found on the palate & tongue			
Hyperplastic – hair-like projections along buccal mucosa; projections cannot be removed with gauze			
Angular Chelitis – ulcerative, crusting lesion at commissure of lip surrounded by mild erythema			Topical creams: ketoconazole, Clotrimazole, mycolog
Oral Hairy Leukoplakia (OHL or HL)			
White, vertically oriented corrugated hyperkeratosis on lateral border of the tongue; caused by Epstein Barr virus (EBV)	Typically presents at CD4+ T cell counts of < 150 cells/mm ³	Usually diagnosed by classical clinical presentation; biopsy & histologic exam or cytologic smear	Often left untreated since OHL is usually asymptomatic; may require concurrent treatment of candida Systemic: acyclovir
Herpes simplex			
Typical blisters & small ulcerations that may take up to a month to heal; multiple lesions may coalesce into large painful lesion; gingival erythema & edema; pain; bleeding	Begin to appear at CD4+ T cell counts of < 100 cells/mm ³	Biopsy, culture, or cytologic smear	Oral: acyclovir; valacyclovir; famciclovir Severe/refractory disease (IV): acyclovir, foscarnet
Aphthous Ulcers			
Circular lesions with white ulcerative centers & erythematous halos; can occur throughout the oral cavity; tend to be extremely painful	typically present at CD4+ T cell counts of < 100 cells/mm ³	Usually diagnosed by clinical appearance; biopsy or culture	Topical (rinses, local applications): Miles Mixture (tetracycline, nystatin, lidocaine, & hydrocortisone mix); dexamethosone elixir; Lidex gel in Orabase B; Dyclone, Benadryl, & Lidocaine mix Intralesional injection: triamcinolone Systemic: thalidomide Severe disease: prednisone
HIV Periodontal Disease			
Linear Gingival Erythema (LGE) – distinct erythematous band along the free gingival margin; petechia on mucosa; many show spontaneous bleeding; can occur even in the presence of good oral hygiene	typically present at CD4+ T cell counts of < 100 cells/mm ³	Usually diagnosed by clinical presentations & lack of response to conventional periodontal therapies	Weekly treatments with local and systemic anti-microbial therapies; aggressive debridement (scaling, root planing) with betadine may be required for 4-to-6 weeks Local: Peridex; tetracycline oral rinse; fluorides Systemic: Metronidazole; clindamycin; amoxicillin clavulanate
Necrotizing Ulcerative Periodontitis (NUP) – rapidly progressing destruction of periodontal tissues; necrosis & ulceration of soft tissue; exposure of underlying bone; sequestration and bone pain; more often occurs in mandibular anterior and posterior molar areas; many show spontaneous bleeding			
Human Papillomavirus (HPV) lesions (warts)			
Typical condylomata or focal epithelial hyperplasia; may appear cauliflower-like, spiky, or slightly raised with a flat surface	warts can occur at any CD4+ T cell count	Usually diagnosed by clinical appearance; biopsy	Surgical or laser excision
Kaposi's Sarcoma (KS)			
Red, blue, or purple lesions that may be macular, papular, or exophytic; occurs more frequently on the palate, tongue, & gingiva; neoplasm of vascular endothelium; cause associated with human herpes virus 8 (HHV8) infection	Can occur at any CD4+ T cell count	Usually diagnosed by clinical appearance that is confirmed by biopsy & histologic exam	Radiotherapy, chemotherapy (systemic or intra-lesional), Interferon, sclerotherapy, surgery

Table 21. Metabolic Complications

- | | |
|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none">• Lipoatrophy• Insulin Resistance• Lactic acidosis | <ul style="list-style-type: none">• Hyperglycemia• Lipid abnormalities• Bone abnormalities |
|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|

- diabetes mellitus
- Hyperlipidemia
- Avascular necrosis
- Osteoporosis/Osteopenia
- Lactic Acidosis

contributor to wasting and appropriate therapy for diarrheal-causing infections as well as symptomatic therapy is important. Unfortunately, ART is a major cause of diarrhea, anorexia, and nausea, and this must also be managed.

Malnutrition has a significant impact on the quality of life of HIV-infected individuals. It also increases the risks of morbidity and mortality. Because wasting is complex, a single approach to management for all patients is unlikely to be successful and an individualized strategy should be employed. All HIV-infected people need early and continuing nutritional assessment and counseling. Referral to a dietician early in the disease process helps many patients deal with nutritional issues. Other referrals (i.e. for mental health counseling or economic assistance) may also be needed. Body composition studies may be required for patients with progressive weight loss. If body fat is proportionally low in relation to total body mass, simply increasing the daily caloric intake may improve the situation. Dietary supplements and appetite stimulation agents, such as megestrol acetate (Megace®) or dronabinol (Marinol®), may be helpful.

Altered Fat Metabolism

Over the past several years, various morphologic and metabolic abnormalities have been described in HIV-infected patients. Although these disorders have been previously referred to collectively as HIV Lipodystrophy Syndrome, this is a heterogeneous group of conditions of varying etiologies:

- Peripheral fat wasting: loss of subcutaneous fat resulting in thin extremities and prominent vein vasculature
- Truncal obesity: increased abdominal visceral fat
- Dorsocervical fat accumulation (“buffalo hump”)
- Lipomas: generally benign fatty tumors
- Gynecomastia: enlargement of breast tissue
- Insulin resistance and/or Type II

The cause of this problem is not known, but several theories exist. In one, successful ART is thought to cause the unwanted side effects and there is, indeed, some data to support the association of PIs and some RTIs with lipodystrophy. Another theory holds that when the viral load is decreased (through successful therapy), the immune system rebuilds itself and, in the process, alters fat metabolism. Yet another theory blames the chronic nature of HIV disease which leads to insulin resistance and altered patterns of fat utilization. Clearly, the cause could be related to HIV disease itself (and is only now becoming obvious as people live longer with the disease), the treatments for the disease, or a combination of these events.

Over time, the prevalence of HIV-related morphologic, metabolic problems is likely to approach 40-60%. While physical body changes are distressing to many patients (and, therefore, of paramount concern), clinical issues also require consideration. In non-HIV-infected populations, hyperlipidemia, truncal obesity, and insulin resistance are associated with increased rates of cardiovascular morbidity and mortality, and these may also be of concern for HIV-infected patients. In addition, sudden death attributed to lactic acidosis has been reported.

Further study is needed to provide guidelines for treatment of these disorders, but general implications for clinical practice include the following:

- Prior to the initiation of ART, patients should be counseled about potential body fat and metabolic changes. An emphasis should be placed on the benefit of ART in relation to reduced viral loads and increased longevity despite the potential for metabolic alterations.
- All patients should have fasting glucose and lipid profiles done prior to beginning ART, especially when the regimen includes a PI. Profiles should be repeated within six-to-eight weeks of the initiation of therapy. Patients currently on therapy should have fasting glucose and lipid profiles analyzed.

Routine periodic assessments of these clinical parameters should be used to guide therapeutic decisions.

- When diabetes or hyperlipidemia occur in the setting of HIV treatment, therapy as indicated in non-HIV clinical settings should be considered and initiated with referral to endocrine and cardiac specialists as needed. Dietary and exercise regimens may be prescribed initially, but medications may be required. Oral anti-diabetic medications and insulin have been used for severe hyperglycemia and lipid and cholesterol lowering medications such as atorvastatin and gemfibrozil have been used to decrease lipid elevations.
- Treatment for osteopenia in females, if indicated, should include calcium supplementation, hormone replacement therapy, and weight-bearing exercise. At this time, there is no evidence to support this intervention in men. Modification of risk factors, such as smoking cessation and decreased alcohol use should also be encouraged.
- Lactic acidosis can occur during treatment with NRTIs and nucleotide RTIs. This complication has not been associated with NNRTIs or PIs alone. While lactic acidosis may occur in the absence of symptoms, when questioned closely, many patients will report some symptoms. The initial clinical presentation may include non-specific gastrointestinal symptoms, such as anorexia, nausea, vague abdominal discomfort or abdominal pain, fatigue, myalgias, shortness of air, and other constitutional complaints. Laboratory evaluation may reveal an increased anion gap, elevated liver aminotransferases, CPK, LDH, amylase and/or lipase. Both clinical symptoms and laboratory abnormalities should raise the index of suspicion for the presence of lactic acidosis. If lactic acidosis is suspected, a venous lactate level should be obtained to confirm this diagnosis. To avoid falsely elevated levels, patients should be well-hydrated, blood should be collected without fist-clenching or use of prolonged tourniquet preparation prior to obtaining blood. Samples should be transported immediately on ice, and processed as soon as they are received in the laboratory. If the lactate level is elevated, this should be repeated to confirm this is a true elevation. For all patients with a confirmed lactate level above 90 mg/dL (10 mmol/L), and for patients who have

symptoms such as those described above and a lactate level above 45 mg/dL (5 mmol/L), all antiretroviral therapy should be discontinued until levels return to normal. Combinations of NNRTIs and PIs may be substituted after the lactate level returns to normal and symptoms resolve. Some experts feel that alternative NRTIs (different from the ones that were being used at the time lactic acidosis developed) may be used, but if so, the patient should be very closely monitored with lactate levels measured periodically for the first few months after re-starting therapy.

Prophylaxis Against Opportunistic Infections

In 1999, the United States Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA) suggested that it may be safe to stop primary or secondary prophylaxis for some (but not all) pathogens. The following section contains general recommendations for common opportunistic infections. Some clinicians advocate prophylaxis for a variety of other opportunistic infections. Referral to expert clinicians and review of the DHHS Guidelines is recommended (see bibliography). Figure 2 represents CD4+ T cell counts at which various opportunistic infections typically occur.

Pneumocystis carinii Pneumonia

Primary prophylaxis is intended to prevent the first episode of PCP and is begun when the CD4+ T cell count is less than or equal to 200-250 cell/mm³, when the CD4+ T cell percent is < 15, or when thrush occurs. All patients who have had prior PCP should also be on prophylaxis (secondary prophylaxis). Oral trimethoprim-sulfamethoxazole (TMP-SMX), one double-strength tablet daily, is the preferred prophylactic intervention, with dapsone, 50-100 mg per day, or inhaled pentamidine, 300 mg aerosolized once a month, as alternatives. Atovaquone (Mepron) is a third alternative, dosed at 750 mg twice a day with a meal high in fat. Lower doses of TMP-SMX (one single strength tablet daily or one double-strength tablet three times a week) may also be effective.

Approximately 10-20% of patients will not tolerate

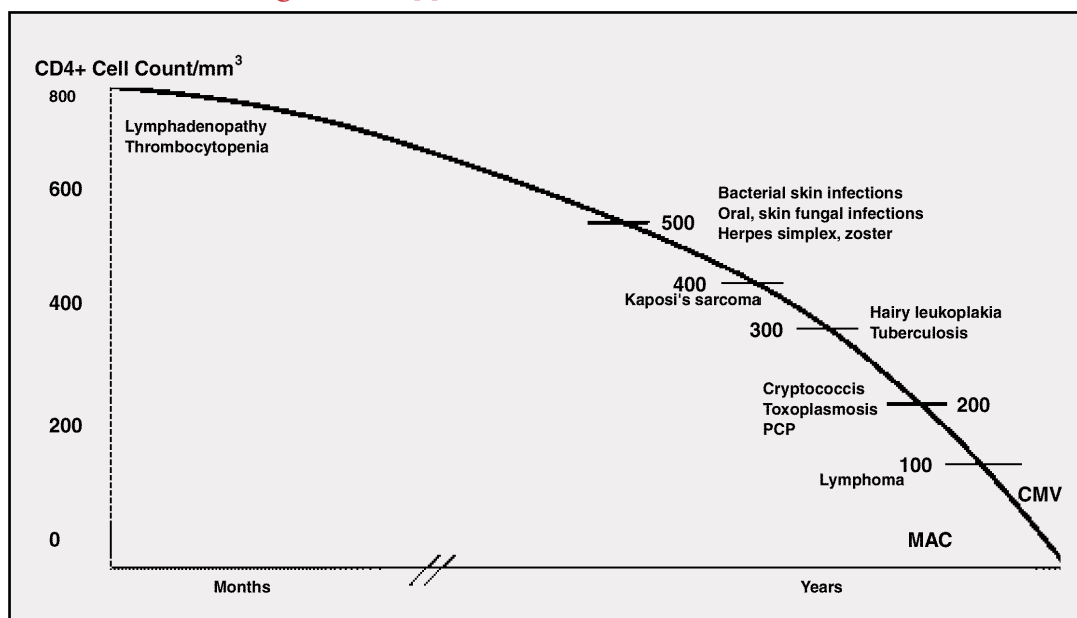
TMP-SMX and develop rash, fever, or elevated liver enzymes. Gradual initiation has been shown to decrease the incidence of rash. TMP-SMX as PCP prophylaxis also appears to provide excellent protection against CNS toxoplasmosis. Dapsone should not be administered if a patient is G6PD deficient.

Inhaled pentamidine prevents only the lung infection with *Pneumocystis carinii* and is not a first line recommendation for prophylaxis. Systemic pneumocystis infection, sparing the lung, have occurred in patients on inhaled pentamidine. Many patients will experience bronchospasm for a day or two following the inhaled pentamidine dose. This can usually be treated

Mycobacterium Avium-Complex (MAC)

The incidence of MAC infection increases about 20% each year after an AIDS-defining diagnosis and is very common for patients with a CD4+ T cell count less than 50 cells/mm³ who are not receiving potent combination ART. Current guidelines recommend prophylaxis for such individuals with either clarithromycin (500 mg twice a day) or azithromycin (1200 mg once a week). The latter is preferred by many specialists because of ease of dosing, lower cost, and fewer drug interactions with PIs. Rifabutin (300 mg/day) is a second line alternative for those unable to take clarithromycin or azithromycin. Seek consultation when using rifabutin, as it is limited by drug interactions, as with many anti-HIV drugs, especially PIs.

Figure 2. Opportunistic Disease Thresholds



symptomatically, but is occasionally severe enough to require discontinuation of the drug. Repeated exposure to pentamidine may be harmful for administering clinicians; inhalation therapy should be done in a respiratory therapy setting that can provide for safe containment of aerosolized and exhaled pentamidine.

Varicella Zoster and Herpes Simplex

Patients who have discomforting recurrences of these herpes infections may require prophylaxis. The doses of acyclovir used may vary, but for herpes simplex, a dose of 400 mg twice a day is usually effective. Alternatives include valacyclovir or famciclovir. For varicella zoster, prophylaxis is more difficult. Consultation with a specialist can help devise the best therapy for this difficult management problem.

Tuberculosis (TB)

Active TB may develop relatively early in HIV infection and has a predilection for extra-pulmonary sites. Because of this, any patient with a positive PPD of at least 5 mm induration or a clear history of an untreated positive PPD should receive 9 months of INH therapy. A two-month course of rifampin or rifabutin plus pyrazinamide therapy has

been shown to prevent TB in HIV-infected patients. Clinicians should explore this option for patients, especially if adherence to the longer course of therapy may be a problem. (See bibliography for tuberculosis treatment guidelines in the presence of HIV infection.)

Toxoplasmosis

Prophylaxis against toxoplasmosis is appropriate for patients who have antibodies to the organism when CD4+ T cell counts drop below 100 cells/mm³. Prophylaxis against toxoplasmosis and PCP can be accomplished with TMP-SMX one double strength tablet 4-7 times/week, or dapsone 50 mg/day and pyrimethamine 50 mg/week plus leucovorin.

Immunizations

Primary prevention of infectious disease through immunization is recommended in many cases (see Table 22) .

Influenza and Pneumococcus

Immunization with Pneumovax and killed influenza vaccine (in season) is appropriate at all stages of HIV. In more advanced HIV disease, the immune response to these antigens may be less than that of an immune competent person, but the immunizations should still be given.

Measles

A discussion of the appropriate age groups for whom measles immunization is recommended is beyond the scope of this sourcebook, but the information can be readily obtained from a local health department. Measles vaccine is a live viral vaccine, but it appears to be safe to administer to patients with HIV infection, even those who have advanced disease. Measles, when it occurs in the wild-type form, can be serious in a person with HIV infection, so if the patient is otherwise eligible for measles vaccine, it may be given.

Table 22. Recommended Vaccines for HIV-infected Persons

Vaccines that are safe if patient is not up-to-date:

- Pneumococcal
- Influenza
- Hepatitis B
- Tetanus toxoid
- Inactivated polio
- MMR (if CD4 > 200)

Vaccines that are safe if needed:

- Hemophilus B
- Cholera
- Inactivated typhoid
- Rabies
- Hepatitis A

Vaccines that are contraindicated:

- BCG
- VZV
- Oral polio
- Oral typhoid
- Yellow fever

Hepatitis Prophylaxis

If the individual has been at risk for hepatitis B infection, which is the case for many HIV-infected patients, then HBV serologic status should be determined. Those who are seronegative should be offered immunization. A discussion of the HIV-infected person who is also a hepatitis carrier (i.e., is hepatitis B surface antigen positive) or is co-infected with Hepatitis B or C is beyond the scope of this sourcebook. Treatment for HBV and HCV is complex and should prompt referral to a specialist. Patients with positive serologies for HBV or HCV should also be encouraged to have the HAV vaccine. Guidelines for prevention of HBV and HCV infection in HIV-infected patients have been published by the USPHS/IDSA (see bibliography). In addition, immunization for hepatitis A is also recommended.

Women and HIV

Epidemiology

The world-wide incidence of HIV in women is now estimated to exceed that of men. In the United States, women of reproductive age are the fastest growing group of people becoming infected with HIV. In the United States, women contributed to over 25% of recently reported AIDS cases. Heterosexual sex is the most commonly reported risk factor/mode of transmission among US women, followed by injection drug use. Since 1996, advances in treatment have dramatically decreased HIV-related morbidity and mortality rates for all groups of infected individuals, but those decreases are smaller for women than for men.

HIV-infected women tend to be young (less than 35 years of age) and of reproductive age; a majority live in low-income households, about half have dependent children, and many are single mothers. Women of color are disproportionately represented in the HIV and AIDS case numbers. Violence, including domestic violence, increases the risk for HIV exposure and infection. When compared to HIV-infected men, HIV-infected women are more likely to be unemployed, more likely to live in poverty, and less likely to have access to health care and insurance.

Clinical Manifestations

Symptoms for primary HIV infection in women tend to be non-specific, including fever, myalgia, arthralgia, diarrhea, vomiting, and lymphadenopathy, and are similar to those found in HIV-infected men. The non-specific nature of these symptoms has lead clinicians to confuse HIV with a vast array of other diseases, especially when HIV is not in the differential diagnosis.

The most common early manifestation of HIV infection in women is recurrent vaginal candidiasis, followed by PGL, bacterial pneumonia, and various constitutional symptoms including fever, night sweats, weight loss, and oral thrush. Significantly, 42% of women in one study had no clinical manifestations of HIV infection during a four-year follow-up after diagnosis. Except for Kaposi's sarcoma, which occurs more often in men who have sex with men, and invasive cervical carcinoma, which occurs exclusively in women, the full spectrum of AIDS-defining illnesses are seen in both sexes.

In one report, abnormal Pap smears were 11 times more common among HIV-infected women than in uninfected women. Screening for cervical dysplasia and malignancy is important since there is growing evidence that the prevalence of cervical dysplasia increases dramatically in HIV, particularly in women with CD4 + T cell counts below 200 cells/mm³ and with evidence of co-infection with the human papilloma virus (HPV). Regular pelvic exams with Pap smears are indicated at six-month intervals for women with low CD4 + T cell counts. Any abnormal Pap smear is an indicator for colposcopy and biopsy.

Pregnancy

Pregnancy has not been confirmed to have an effect on the clinical progression of HIV disease when compared to the expected effects of time and stage of disease. The effect of repeated pregnancies on disease progression remains to be determined. Perinatal transmission of HIV occurs in about 25% of deliveries when the mother is infected and does not use ART. Most transmission occurs close to or during the delivery process when the infant has contact with the mother's blood and vaginal secretions. Perinatal transmission can also occur after delivery through breast feeding.

Increased risk of perinatal transmission is associated with low CD4 + T cell counts, positive p24 antigen tests, high viral loads, maternal drug or alcohol use, breaks in the placental barrier (associated with STDs and chorioamnionitis), advancing maternal HIV disease, and prolonged premature rupture of the membranes. A study of ZDV in prevention of vertical HIV transmission (ACTG 076) showed a decrease in transmission rates from 25% to 8%. Further research has shown that ART appropriate to maternal need during pregnancy, intravenous ZDV during labor and delivery, and six weeks of ZDV therapy for the newborn can significantly reduce the rate of perinatal HIV transmission. Studies of combination ART used during pregnancy have shown transmission rates close to zero. Currently, the CDC recommends that all pregnant women be assessed for risk for HIV and offered antibody testing, that those found to be infected be offered appropriate ART, and that the newborn receive follow-up treatment and evaluation.

In the event that optimal ART during pregnancy is not used, two maternal doses of nevirapine (one early in labor and one at the beginning of delivery) followed by a single newborn dose during the first 48 hours of life has been shown to significantly reduce perinatal transmission rates although not as effectively as optimal combination ART.

Treatment options vary and there are positive as well as potentially negative consequences of ART during pregnancy. Because of this, decisions about therapy should be made by the pregnant woman with the assistance of her clinician after full disclosure of the available data. Consult the current guidelines (see bibliography) and HIV-experienced clinicians for treatment recommendations.

Psychosocial Issues in the care of the HIV-Infected Patient

More than any disease in recent history, HIV infection brings into focus the relationship between illness and its psychological and social ramifications. People living with HIV infection are confronted with severe illnesses, neuropsychiatric disorders, overwhelming societal responses, and complex social and psychological needs.

This multidimensional disease challenges not only the individual infected with HIV, but also people whose lives are indirectly touched by the epidemic. Table 23 outlines some of the issues faced by the person living with HIV and Table 24 lists psychosocial issues for family members and significant others, as well as the HIV-infected individual.

New psychosocial issues are emerging with the widespread use of powerful and effective combination therapies. For those who have access to the drugs and for whom the drugs work, dramatic improvement in health status and survival occur. Individuals once focused on dying may find themselves concerned about the issues of living with a chronic disease. For many, this comes as a shock and may create the need to mend relationships, to return to work, to consider long term financial planning, to reassess life goals, and/or to completely change decisions that were made when the expected life span was limited.

For others, new drug therapies do not bring hope. For those who cannot access the drugs or for whom the drugs show no benefit, the result may be despair, grief, anger, guilt, or a fatalistic outlook. These individuals need support and education about future treatment options to maintain hope.

A major psychosocial issue brought about by the advent of new treatment protocols is the need to adhere to prescribed treatment regimens. These regimens are often complex and confusing; difficult to schedule; require a high degree of knowledge, skill, and personal commitment; cause unique and different side effects; will, at least according to current research, be prescribed for the rest of the patient's life; and taking them can potentially compromise a person's confidentiality in social or work settings. These conditions, superimposed on social, economic, familial, cultural, spiritual, and psychological factors in the HIV-infected person's life, can result in a situation where consistent adherence will be difficult. Clinicians must be constantly aware of these issues in order to assess problems and work with the client to solve them. Consultation and referral to various team members, including physicians, nurses, social workers, case managers, counselors, and educators, should occur routinely.

Table 23. Psychosocial Issues for the Patient with HIV Infection

Physical

- decrease of physical strength
- hospitalizations
- sexuality
- locating professional providers
- changes and disturbances in body image
- fatigue
- adherence to treatment regimens
- substance use

Emotional

- self-esteem
- independence/control
- hopelessness/despair
- uncertainty
- anxiety
- self-blame
- depression
- anger
- fear
- sadness
- loss of dreams and future plans
- embarrassment
- guilt
- shock
- grief
- denial

Social

- finances
- friends/family
- relationships
- sexuality
- leisure
- social support
- discrimination/stigma

Spiritual

- life meanings
- death
- suicide
- forgiveness
- acceptance/hope
- spiritual practice and connection

Table 24. Psychosocial Issues for Family Members and Significant Others of Persons Living with HIV/AIDS

Social isolation may develop because of:

- Stigma or perceived stigma of HIV or risk behaviors
- Rejection by family, friends

An additional crisis may occur

if the family discovers homosexuality, bisexuality, infidelity, or drug use at the same time that they learn of the HIV infection.

Fear related to:

- Contagion
- Disability, chronic disease
- Death and dying

Anticipated and real losses:

- Decrease in social support system
- Death of child/family member may create a "death out of order" situation in which parents have to deal with the death of a child
- Parental dreams and expectations
- Physical and cognitive changes in family member
- Loss or alteration in personal and family lifestyle and goals

Confusing emotions typically seen in grief reactions:

- Anger
- Guilt
- Sadness/depression
- Blame
- Shame
- Anxiety/panic

Caretaking concerns:

- Helplessness - What can be done and what are best ways to help?
- Intrusion on family's lifestyle:
 - Demands on time, energy, abilities
 - Shifting of family roles
- Negotiation of health care systems
- Home care versus hospital care

Family Issues

- Re-emergence of past family conflicts
- Conflicts with patient's lover/friends/family
- Financial burdens
- Sibling concerns (dependent on age and maturity):
 - Fears may be related to contagion, having physical contact with affected siblings, or being rejected by friends, etc.
 - Guilt related to feeling responsible for sibling's illness, "escaping" the illness, or wishing the ill sibling harm
 - Needs of healthy siblings may be ignored by parents, health care workers, friends, and relatives.

Treat the Exposure Site

Wash the areas exposed to potentially infectious fluids with soap and water as soon as possible after the exposure. Do NOT apply caustic agents or inject antiseptics or disinfectants into the wound. Exposed mucous membranes should be flushed with water and exposed eyes should be flushed with saline solution.

Report and Document

Report all occupational exposures immediately. Reports need to include the following:

- Date and time of exposure
- Details of the incident: where and how the exposure occurred, exposure site(s) on the HCP's body; if related to sharp device, the type and brand of device should be recorded
- Details of the exposure: type and amount of fluid or material, severity of the exposure
- Document counseling, postexposure management and follow-up
- Details about the exposure source: whether the source material contained HIV, if source patient is HIV-infected, determine stage of disease, viral load, history of antiretroviral therapy, and antiretroviral resistance information if known
- Details about the exposed HCP: hepatitis B vaccination and vaccine-response status, other medical conditions and medication

Record circumstances of the exposure and PEP management in the exposed HCP's confidential medical record.

Evaluate the Exposure

Evaluate the exposure for potential to transmit HBV, HCV, or HIV based on the type of body substance involved, and the route and severity of exposure. Exposures to any of the following through percutaneous injury or contact with a mucous membrane are situations that cause a risk for blood borne transmission and require further evaluation:

- Blood
- Semen
- Cerebrospinal fluid
- Pleural fluid
- Peritoneal fluid
- Synovial fluid
- Vaginal secretions
- Pericardial fluid
- Amniotic fluid

Consider the following factors when assessing the need for follow-up:

- Type of exposure
- Type and amount of fluid/tissue
- Infection status of source patient
- Susceptibility of exposed HCP

Evaluate the Exposure Source

If the source patient is known, test the patient for HBsAg, HCV antibody, and HIV antibody. For patients who cannot be tested, consider medical diagnoses, clinical symptoms, and history of risk behaviors. If source patient is NOT known, evaluate the likelihood of high risk exposure. Do not test discarded needles for blood borne pathogens, as the reliability of these findings is not known.

PEP Management

Start HIV PEP immediately (optimal timeframe of 1-4 hours after exposure). If the delay lasts more than 36 hours, seek expert consultation. PEP should continue for four weeks, if tolerated. Typical choices for PEP are:

- A basic 2-drug regimen, appropriate for most exposures
- An expanded 3-drug regimen, for exposures that pose an increased risk of infection.

If questions remain about the extent of risk, starting the basic, 2-drug PEP is better than delaying administration.

Drug Selection

For all HCP exposures to known or suspected HIV-infected sources, PEP regimen should be initiated promptly and carried out for 28 days. Anticipate medication side effects and provide appropriate symptomatic management.

Recommended Regimens*

2-drug combinations:

3-drug combinations:

AZT 300mg BID	+	3TC 150mg BID	When initiating expanded regimen, expert consultation is recommended. Typical regimens include the basic regimen plus a protease inhibitor. Additional medications are rarely used.
3TC 150mg BID	+	d4T 40mg BID	
d4T 40mg BID	+	ddl 400mg QD on empty stomach	

*Decisions should be made based in part on information about the source patient including antiretroviral therapy, response to therapy including viral load, CD4 count, current disease stage, and any data on HIV resistance testing. Delays in getting information should NOT delay initiation of PEP and modifications can be made.

HIV PEP FOR PERCUTANEOUS INJURIES

EXPOSURE TYPE	Infectious Status of Source				
	HIV-Infected Class 1	HIV-Infected Class2	Source of Unknown HIV Status	Unknown Source	HIV-Negative
	e.g., Asymptomatic HIV infection or unknown viral load (e.g. < 1,500 RNA copies/mL)	e.g., Symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load*	e.g., Source patient refuses testing or is unavailable	e.g., Needle from sharps container	
Less Severe - Solid needle - Superficial injury	Recommend basic 2-drug PEP	Recommend expanded 3-drug PEP	Generally no PEP warranted; Consider basic 2-drug PEP ¹ for source with HIV risk factors ²	Generally no PEP warranted; Consider basic 2-drug PEP ¹ in settings where exposure to HIV-infected persons is likely	No PEP warranted
More Severe - Large-bore, hollow needle - Deep puncture - Visible blood on device - Needle used in patient's artery or vein	Recommend expanded 3-drug PEP	Recommend expanded 3-drug PEP	Generally no PEP warranted; Consider basic 2-drug PEP ¹ for source with HIV risk factors ²	Generally no PEP warranted; Consider basic 2-drug PEP ¹ in settings where exposure to HIV-infected persons is likely	No PEP warranted

¹The designation "consider PEP" indicates that PEP is optional and should be based on an individualized decision between the exposed person and the treating clinician.

²If PEP is initiated and the source is later determined to be HIV-negative, PEP should be discontinued.

*Seek expert consultation if drug resistance is a concern. Initiation of PEP should NOT be delayed pending expert consultation.

HIV PEP FOR MUCOUS MEMBRANE AND NONINTACT SKIN EXPOSURES

EXPOSURE TYPE	Infectious Status of Source				
	HIV-Infected Class 1	HIV-Infected Class2	Source of Unknown HIV Status	Unknown Source	HIV-Negative
	e.g., Asymptomatic HIV infection or unknown viral load (e.g. < 1,500 RNA copies/mL)	e.g., Symptomatic HIV infection, AIDS, acute sero-conversion, or known high viral load*	e.g., Source patient refuses testing or is unavailable	e.g., Blood spill or bloody equipment that cannot be traced to a patient	
Small Volume - A few drops	Consider basic 2-drug PEP	Recommend basic 2-drug PEP	Generally no PEP warranted; Consider basic 2-drug PEP ¹ for source with HIV risk factors ²	Generally no PEP warranted; Consider basic 2-drug PEP ¹ in settings where exposure to HIV-infected persons is likely	No PEP warranted
Large Volume - Large blood splash	Recommend basic 2-drug PEP	Recommend expanded 3-drug PEP	Generally no PEP warranted; Consider basic 2-drug PEP ¹ for source with HIV risk factors ²	Generally no PEP warranted; Consider basic 2-drug PEP ¹ in settings where exposure to HIV-infected persons is likely	No PEP warranted

¹The designation "consider PEP" indicates that PEP is optional and should be based on an individualized decision between the exposed person and the treating clinician.

²If PEP is initiated and the source is later determined to be HIV-negative, PEP should be discontinued.

*Seek expert consultation if drug resistance is a concern. Initiation of PEP should NOT be delayed pending expert consultation.

Follow Up

HIV-antibody testing should be repeated at 6 weeks, 3 months and 6 months post exposure. Extended follow-up (12 months) is recommended for HCP who become infected with HCV following an exposure to a source co-infected with HIV and HCV. Clinician should counsel exposed HCP about the signs and symptoms of acute retroviral syndrome (flu-like syndrome), and the need to come in for additional testing at the onset of symptoms. If PEP is given, HCP should be monitored for drug toxicity. A CBC, renal function tests, and hepatic function tests should be done at baseline (within 72 hours) and at 2 weeks. Exposed HCP should refrain from donating blood, plasma, organs, tissue, or semen and utilize harm reduction methods such as using latex barriers during sex and not sharing injection equipment. Mental health counseling should also be offered as needed.

Exposed HCP should be counseled to protect sex and needle sharing partners until HIV infection has been ruled out. Harm reduction techniques including latex barriers during sex, and not sharing injection equipment can be used during counseling. HCP should also be counseled about the signs and symptoms of acute retroviral syndrome (flu-like syndrome), the need to report it, and to come in for follow-up testing at the time symptoms appear.

Special Considerations

Expert consultation in providing HIV PEP is recommended in the following situations:

- Delayed exposure report (later than 24-36 hours)
- Unknown source (e.g. needle from sharps container)
- Known or suspected pregnancy of exposed HCP

While most drugs used in HIV therapy have not been found to be a problem in pregnancy, new information comes out all the time. There are now recommendations against using efavirenz, ddI and d4T in pregnant women. Consultation with an HIV expert clinician is recommended. Pregnancy does not preclude the use of optimal PEP regimens, nor should PEP be denied solely on the basis of pregnancy.

- Resistance of the source virus to antiretroviral agents

Selection of drugs to which the source patient's virus is unlikely to be resistant is recommended, if the source patient's virus is known or suspected to be resistant to more than one of the drugs considered for the standard PEP regimen. Resistance testing of the source patient's virus at the time of exposure is not recommended.

- Toxicity of the initial PEP regimen

Adverse symptoms such as diarrhea, and headaches are common with PEP. These can often be managed without changing the PEP regimen by prescribing antimotility and/or antemetic agents. Consultation may be obtained when side effects are difficult to manage. If the use of nevirapine on initial PEP regimen is being considered, also seek expert consultation

PEP RESOURCES	
National Clinicians' Postexposure Prophylaxis Hotline (PEpline)	1-888-448-4911 www.ucsf.edu/hivcntr
National HIV Telephone Consultation Service	1-800-933-3413
Centers for Disease Control and Prevention (CDC) Report occupationally acquired HIV infections and failures of PEP	1-800-893-0485
HIV Antiretroviral Pregnancy Registry	1-800-258-4263
Food and Drug Administration Report unusual or severe toxicity to antiretroviral agents	1-800-332-1088 www.fda.gov/medwatch
HIV/AIDS Treatment Information Service	www.hivatis.org
Needlestick!	www.needlestick.mednet.ucla.edu
Hepatitis Hotline	1-888-443-7232 www.cdc.ov/hepatitis

Appendix B: Nucleoside Reverse Transcriptase Inhibitors (NRTI)

Drug Name Abbreviation (Trade Name®)	Available Dosage Forms	Usual Dose*	Special Dosing Considerations	Common Adverse Effects Serious Adverse Effects
zidovudine ZDV, AZT (Retrovir®)	100 mg capsules 300 mg tablets 50 mg/5 ml syrup	300 mg q12h	Take with food to lessen gastrointestinal side effects.	nausea, vomiting, anemia, leukopenia myopathy, lactic acidosis with hepatic steatosis, lipodystrophy†
didanosine ddl (Videx®)	125, 200, 250, 400 mg delayed release capsules 100, 167, 250 mg buffered powder packets for oral solution 2 gm, 4 gm powder for suspension 25, 50, 100, 150, 200 mg chewable tablets	Delayed Release Caps: (≥60 kg) 400 mg q24h (< 60 kg) 250 mg q24h Powder packets: (≥60 kg) 250 mg q12h (< 60 kg) 167 mg q12h Suspension: (≥60 kg) 200mg q12h (< 60 kg) 125mg q12h Chewable tablets: (≥60 kg) 200mg q12h or 400 mg q24h (< 60 kg) 125mg q12h	All didanosine preparations must be taken on an empty stomach, at least 30 minutes before or 2 hours after eating. A minimum of 2 chewable tablets per dose is needed to assure adequate buffering of stomach acid.	nausea, diarrhea, peripheral neuropathy pancreatitis, hepatitis, lactic acidosis with hepatic steatosis, lipodystrophy†
zalcitabine ddC (Hivid®)	0.375 mg tablets 0.75 mg tablets	0.75 mg q8h	Take with or without food.	oral ulcers, peripheral neuropathy pancreatitis, lactic acidosis with hepatic steatosis, lipodystrophy†
stavudine d4T (Zerit®)	15, 20, 30, and 40 mg capsules 1 mg/ml oral solution	(≥60 kg) 40 mg q12h (< 60 kg) 30 mg q12h	Take with or without food. Dosage reduction may be effective for severe peripheral neuropathy.	peripheral neuropathy pancreatitis, lactic acidosis with hepatic steatosis, lipodystrophy†
lamivudine 3TC (Epivir®)	10 mg/ml oral solution 150 mg tablets	(> 50 kg) 150 mg q12h (< 50 kg) 2 mg/kg q12h	Take with or without food.	nausea, nasal congestion lactic acidosis with hepatic steatosis, lipodystrophy†
ZDV + 3TC (Combivir®)	combination tablet (300 mg AZT and 150mg 3TC)	1 tablet q12h	Take with or without food.	See individual agents.
abacavir (Ziagen™)	300 mg tablets 20 mg/ml oral solution	300 mg q12h	Take with or without food. hypersensitivity reaction: signs/symptoms are rash or one or more from at least 2 of the following groups: • fever • nausea, vomiting, diarrhea, abdominal pain • extreme tiredness, achiness, generally ill feeling • sore throat, shortness of breath, cough If signs/symptoms of the reaction occur: • Stop abacavir immediately • Do NOT restart: abacavir rechallenge has been associated with fatal hypotension	nausea, lipodystrophy†
AZT + 3TC + abacavir (Trizivir™)	combination tablet (300 mg AZT, 150 mg 3TC, and 300 mg abacavir)	1 tablet q12h	See individual agents.	See individual agents.
Nucleotide Reverse Transcriptase Inhibitor				
tenofovir DF (Viread®)	300 mg tablet	1 300 mg tablet once daily	Take after a meal.	nausea, vomiting

*Usual doses are provided. Doses may vary based on weight, the presence of renal or hepatic failure.

†The association of NRTIs with fat redistribution syndromes is unclear.

Metabolism of NRTIs AZT-hepatic via glucuronidation; ddl-unknown, however, 55% renally eliminated as unchanged drug; ddC-renally eliminated; d4T-unknown, however, 40% renally eliminated as unchanged drug; 3TC-renally eliminated; abacavir-hepatic via alcohol dehydrogenase and glucuronyl transferase

Medications that may have Clinically Significant Drug Interactions with NRTIs*

AZT - acetaminophen, cimetidine, indomethacin, lorazepam, probenecid, aspirin, cytotoxic drugs, drugs that interfere with RBC/WBC, d4T
ddl - pentamidine, drugs that cause pancreatitis/peripheral neuropathy, separate doses by at least 2 hours with indinavir, quinolones, tetracyclines, ketoconazole, itraconazole, dapsone

ddC - probenecid, aminoglycosides, amphotericin, foscarnet, cimetidine, d4T, ddl, 3TC, drugs that cause peripheral neuropathy/pancreatitis
d4T - zidovudine, drugs that cause peripheral neuropathy/pancreatitis
abacavir - ethanol

*This list is not all inclusive.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Drug Name Abbreviation (Trade Name®)	Available Dosage Forms	Usual Dose*	Special Dosing Considerations	Common Adverse Effects ----- Serious Adverse Effects
nevirapine NVP (Viramune®)	200 mg tablets 50 mg/5 ml oral suspension	200 mg q24h for 14 days, then 200 mg q12h thereafter	Induces the metabolism of certain drugs, therefore, the dosages of co-administered protease inhibitors may need to be increased.	Rash ----- erythema multiforme, hepatotoxicity
delavirdine DLV (Rescriptor®)	100 and 200 mg tablets	400 mg q8h (600 mg q12h dosing not yet approved by the FDA)	Space doses one hour apart from antacids and didanosine chewable tablets, suspension, and oral solution Inhibits the metabolism of certain drugs, therefore, the dosages of selected protease inhibitors may need to be decreased.	Rash, liver function changes ----- erythema multiforme
efavirenz EFV (Sustiva™)	50, 100, and 200 mg capsules	600 mg qd at bedtime	May take with or without food, however, avoid taking with foods high in fat. Induces the metabolism of certain drugs, therefore, the dosages of co-administered protease inhibitors may need to be increased. Should not be administered during pregnancy.	Rash, drowsiness, dizziness, trouble concentrating, unusual dreams ----- confusion, encephalopathy
*Usual doses are provided. Doses may vary based on weight, the presence of renal or hepatic failure, or when using combinations which have pharmacokinetic interactions.				

Metabolism of NNRTIs

- Nevirapine:** cytochrome P450 metabolism primarily by isoenzymes from the CYP3A family; causes induction of CYP3A isoenzymes
- Delavirdine:** cytochrome P450 metabolism primarily by isoenzymes from the CYP3A family although CYP2D6 may play a minor role; causes inhibition of CYP3A and CYP2D6 isoenzymes
- Efavirenz:** cytochrome P450 metabolism primarily by isoenzymes CYP3A4 and CYP2B6; causes induction of CYP3A4 isoenzyme; causes inhibition of CYP2C9, 2C19, and 3A4 isoenzymes

Medications that should NOT be Coadministered with NNRTIs

- Nevirapine:** St. John's Wort
- Delavirdine:** rifampin, astemizole, cisapride, pimozone, midazolam, triazolam, alprazolam, amiodarone, quinidine, ergotamine derivatives, bepridil, flecainide, propafenone, St. John's Wort, simvastatin, lovastatin
- Efavirenz:** rifampin, astemizole, cisapride, pimozone, midazolam, triazolam, ergotamine derivatives, St. John's Wort

Medications that have clinically significant Drug Interactions with NNRTIs - Avoid Use or Modify Dosages*

- Nevirapine:** rifampin, rifabutin, ketoconazole, oral contraceptives, methadone, protease inhibitors
- Delavirdine:** warfarin, carbamazepine, phenobarbital, phenytoin, clarithromycin, dapson, ketoconazole, rifabutin, calcium channel blockers, sildenafil, cerivastatin, atorvastatin, selective serotonin reuptake inhibitors, bupropion, nefazadone, clonazepam, ethosuximide, sedative/hypnotics, amphetamines, protease inhibitors, didanosine, antacids, H-2 receptor antagonists, dihydropyridines, amphotericin
- Efavirenz:** protease inhibitors, ethinyl estradiol, warfarin, rifabutin, phenobarbital, phenytoin, carbamazepine, clarithromycin

*This list is not all inclusive.

Protease Inhibitors

Drug Name Abbreviation (Trade Name®)	Available Dosage Forms	Usual Dose*	Special Dosing Considerations	Common Adverse Effects ----- Serious Adverse Effects
saquinavir SQV (Fortovase™ (F)) (Invirase® (I))	F – 200 mg soft gel capsule	F – 1200 mg q8h I – 600 mg q8h	F – Take with food and refrigerate capsules. (OK to keep at controlled room temperature for 90 days.)	diarrhea, nausea
	I – 200 mg hard gel capsule	Often used at lower doses with ritonavir	I – Take within 2 hours of a high fat meal.	diabetes, hyperlipidemia, lipodystrophy†
ritonavir RTV (Norvir®)	100 mg capsule	600 mg q12h	Take with food.	nausea, vomiting, diarrhea, taste perversion, perioral and circumoral paresthesia
	80 mg/ml liquid	Often used at lower doses to increase levels of other protease inhibitors	Capsules must be refrigerated but may be stored at controlled room temperature for 30 days.	hepatitis, diabetes, hyperlipidemia, lipodystrophy†
indinavir IDV (Crixivan®)	200 mg capsule	800 mg q8h	Take on empty stomach or with a light meal or a low fat snack. May be taken with food if given with ritonavir.	nausea, diarrhea, increase indirect bilirubin
	333 mg capsule	May be used at lower doses with ritonavir	Drink 1.5L water each day.	diabetes, lipodystrophy†, hyperlipidemia, interstitial nephritis, nephrolithiasis
	400 mg capsule		Take 1 hour before or 2 hours after didanosine chewable tablets, suspension, or oral solution.	
nelfinavir NFV (Viracept®)	250 mg tablet	1250 mg q12h	Take with food.	diarrhea, flatulence, nausea,
	50 mg/gram oral powder			diabetes, hyperlipidemia, lipodystrophy†
amprenavir APV (Agenerase™)	50 mg soft gel capsule	1200 mg q12h	Take on empty stomach or with light snack. Avoid taking with high fat foods.	nausea, vomiting, headache, taste perversion, rash, perioral paresthesia
	150 mg soft gel capsule	May be used at lower doses with ritonavir	All formulations contain a very high quantity of Vitamin E. Advise patients to not take supplemental Vitamin E.	severe skin rashes, hyperlipidemia, lipodystrophy†
	15 mg/ml oral solution			
lopinavir/ ritonavir (Kaletra™)	133.3mg/33.3mg capsules	400 mg/100 mg or 3 capsules q12h	Take with food.	nausea, diarrhea, taste perversion, perioral and circumoral paresthesia,
	80mg/20mg per 1.0 ml oral solution	(4 capsules q12h with efavirenz or nevirapine)	Capsules and solution must be refrigerated but may be stored at controlled room temperature for 60 days.	hepatitis, diabetes, hyperlipidemia, lipodystrophy†
*Usual doses are provided. Doses may vary based on weight, the presence of renal or hepatic failure, or when using combinations that have pharmacokinetic interactions.			†The association of PIs with fat redistribution syndromes is unclear.	

Metabolism of Protease Inhibitors

All of the protease inhibitors are metabolized by the cytochrome P450 enzyme system, primarily by the isoenzyme CYP3A4. All protease inhibitors inhibit the isoenzyme CYP3A4. The degree of inhibition is dependent on the particular protease inhibitor being used with ritonavir producing the greatest inhibition of the isoenzyme. Ritonavir induces the isoenzyme CYP1A2 and also inhibits CYP2A6, 2C9, 1A2, 2C19, 2D6, and 2E1. Lopinavir/ritonavir inhibits CYP2D6.

Medications that should NOT be Coadministered with Protease Inhibitors

rifampin, astemizole, cisapride, pimozide, midazolam, triazolam, amiodarone, quinidine, ergotamine derivatives, bepridil, flecainide, propafenone, St. John's Wort, simvastatin, lovastatin

Medications that have Clinically Significant Drug Interactions with Protease Inhibitors - Avoid Use Or Modify Dosages*

efavirenz, nevirapine, delavirdine, warfarin, carbamazepine, phenobarbital, phenytoin, clarithromycin, ketoconazole, itraconazole, rifabutin, dihydropyridine calcium channel blockers, dexamethasone, prednisone, sildenafil, atorvastatin, cerivastatin, cyclosporine, tacrolimus, rapamycin, methadone, ethinyl estradiol, tricyclic antidepressants, selective serotonin reuptake inhibitors, bupropion, nefazadone, meperidine, theophylline, verapamil, diltiazem, propoxyphene, tramadol, mexilitine, disopyramide, lidocaine, clonazepam, ethosuximide, dronabinol, quinine, metoprolol, timolol, perphenazine, risperidone, thioridazine, sedative/hypnotics, stimulants

*This list is not all inclusive. The presence of an interaction and the degree of the drug interaction are dependent on the particular protease inhibitor being used.

National AIDS Services, Hotlines and On-Line Resources

AEGIS (AIDS Education Global Information System) www.aegis.com

The world's largest HIV knowledge base, featuring all the best newsletters, HIV news from top newspapers and wire services, and search capability for all documents.

AIDS.org www.aids.org

This global network provides up-to-date information and links to HIV-focused web sites.

AIDS Clinical Trials Information Service www.actis.org

Provides current information on clinical trials, study protocols, study locations, patient enrollment and eligibility, study results, and database searches.

In Canada and the United States
1-800-TRIALS-A (1-800-874-2572)

AIDS InfoNet www.aidsinfonet.org

Provides fact sheets on treatments, prevention, social services, and web resources. Easy to print, appropriate for patient and clinician education, and updated on a regular basis. Available in English and Spanish.

American Foundation for AIDS Research (AmFAR) www.amfar.org

Provides information about basic science research, clinical research and information, and public policy programs.
(212) 806-1600

Association of Nurses in AIDS Care (ANAC) www.anacnet.org

Organization of U.S. nurses specializing in HIV care. Offers networking, information exchange, social awareness, and advocacy for people living with HIV.
1-800-260-6780

CDC National Prevention Information Network www.cdcnpin.org/

A national reference, referral, and distribution service for HIV-related information. Services include comprehensive reference and referral services, publications distribution services, resource centers, free on-line and Internet services, clinical trials information and HIV/AIDS treatment information. CDC NAC FAX is a 24-hour, on-demand service that quick faxes documents and other information. Available documents include HIV Prevention Fact Sheets, MMWRs, global and domestic AIDS surveillance statistics, Spanish language materials and other resources.
1-800-458-5231

Healthcare Consortium www.hivcme.org

The Healthcare Consortium is a non-profit organization that provides educational programming through conferences and on its web page. Areas of interest include women and HIV, adolescent issues, HIV in prisons, and treatment issues.

HIV/AIDS Treatment Information Service (ATIS) www.hivatis.org

Information about federally approved HIV/AIDS treatment options and links to other key HIV/AIDS information resources. All calls are confidential. Offered by the US Public Health Service.
1-800-HIV-0440 (1-800-448-0440)

HIV Dent www.hivdent.org

Several sections on the oral manifestations of HIV disease and a large picture gallery. Also, information on infection control, post-exposure protocols, pediatric/adolescent care, medications, funding and other resources.

HIV InSite www.hivinsite.org

Sponsored by the University of California at San Francisco. The site provides excellent search capabilities in a broad spectrum of science, prevention, and treatment arenas.

HIV Telephone Consultation Service for Health Care Providers www.ucsf.edu/hivcntr

A national HIV telephone consultation service for clinicians who have questions about HIV care practices. A physician, nurse practitioner, and pharmacist from San Francisco General Hospital staff the consultation line. It is a useful resource for rural clinicians practicing in sites where HIV expertise is not readily available.
1-800-933-3413

National Clinicians' Post-Exposure Prophylaxis Hotline (PEPLINE) www.ucsf.edu/hivcntr

A 24-hour hotline providing prompt and up-to-date information for clinicians who need advice on treating health care workers who have suffered occupational exposures to blood borne pathogens. On-line information on post-exposure prophylaxis information is available on PEPnet.
1-800-HIV-4911 (1-800-448-4911)

National Hemophilia Foundation (NHF) www.hemophilia.org

The NHF is the leading U.S. volunteer agency dedicated to improving the health and welfare of people with hemophilia, von Willebrand disease, and other coagulation disorders, as well as their complications, including HIV.
(212) 328-3700

National Minority AIDS Council (NMAC) www.nmac.org

A national AIDS organization that develops programs and services for community-based organizations serving people of color affected by HIV/AIDS. Programs include: U.S. Conference on AIDS, research and treatment information, and technical assistance to health departments and community planning groups.
(202) 483-6622 (202)-438-NMAC

National Native American AIDS Prevention Center www.nnaapc.org

An organization providing information on HIV and related diseases among American Indians, Alaska natives, and native Hawaiians.
(510) 444-2051

National Pediatric and Family HIV Resource Center www.pedhivaid.org

Provides material concerning the care of children and families living with HIV, current fact sheets on HIV in women and children, catalog of available books and videos.
1-800-362-0071

Project Inform www.projinf.org

An HIV treatment information organization working on behalf of people living with HIV infection. Provides information on treatment, research and advocacy issues. Operates the Project Inform National HIV/AIDS Treatment Hotline. Staffed by volunteers who confidentially answer questions about HIV treatment and related diseases.
1-800-822-7422

MPAETC E-Mail Consultation Service for HIV Infection

Clinicians treating patients with HIV infection may access an e-mail-based electronic consultation service with questions about diagnosis, treatment, and management of HIV.

Why an e-mail consultation service specific to HIV infection?

- Information about HIV infection and AIDS is expanding so rapidly that only the most invested clinicians can keep up.
- Morbidity and mortality in HIV can be reduced when the most up-to-date care is provided.
- As new therapies, resources, and information about HIV develop, clinical care becomes more complex.
- A fast, easily accessible consultation resource can support delivery of the best care possible.

How does e-mail consultation work?

- The clinician sends questions to the e-mail address.
- Questions are reviewed by HIV-expert consultants.
- A response is generated and sent back to the inquirer.
- Frequently asked questions (FAQs) and responses to those questions will be published on the MPAETC web page:
www.uchsc.edu/sm/aids

How to access consultation service:

Contact the Mountain Plains AIDS Education and Training Center at:

hivconsultation@uchsc.edu

How is confidentiality assured?

- Clinicians are asked to word questions in a manner that protects the patient's identity.
- **No names** should be transmitted with questions.
- Questions and responses stay within the system.
- Publications of FAQs will remove any identifiers, including state of residence, clinician name, and patient identifiers that are not essential to the case.

Patient Assistance Programs for HIV Medications

Pharmaceutical companies that have medication assistance programs for HIV-infected patients who are unable to afford the cost of their medications are listed below. Eligibility requirements vary from program to program, some assess need on a case-by-case basis and many require the application for assistance be initiated by a physician. For more information contact the companies directly.

Drug Name	Brand Name	Manufacturer	Telephone
Lamivudine (3TC)	Epivir®	GlaxoSmithKline	800-272-4878
Zidovudine (AZT, ZDV)	Retrovir®		
Abacavir (ABC)	Ziagen™		
AZT + 3TC	Combivir®		
AZT + 3TC + ABC	Trizivir™		
Amprenavir (APV)	Agenerase®		
Didanosine (ddI)	Videx®	Bristol-Myers Squibb Company	800-272-4878
	Videx EC®		
Efavirenz (EFV)	Sustiva™		
Stavudine (d4T)	Zerit®		
Zalcitabine (ddC)	HIVID®	Roche	800-282-7780
Saquinavir (SQV) Soft gel capsules	Fortovase™		
Hard gel capsules	Invirase®		
Delavirdine (DLV)	Rescriptor®	Agouron	888-777-6637
Nelfinavir (NFV)	Viracept®	Pharmaceuticals, Inc.	
Nevirapine (NVP)	Viramune®	Boehringer Ingelheim	800-556-8317
Lopinavir/Ritonavir	Kaletra™	Abbott Laboratories	800-222-6885
Ritonavir (RTV)	Norvir®		
Indinavir (IDV)	Crixivan®	Merck & Co., Inc.	800-850-3430
Tenofovir	Viread®	Gilead	800-226-2056

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- Centers for Disease Control and Prevention (CDC)
Guidelines available from all AETC offices and at www.cdc.gov/hiv/pubs/guidelines.htm
- Revised guidelines for HIV testing, counseling, and referral* (February 18-19, 1999).
- Revised recommendations for HIV screening of pregnant women* (April 26-29, 1999).
- HIV partner counseling and referral services* (December, 1998).
- Clarke, S., Harrington, P., Barry, M., & Mulcahy, F. (2000). The tolerability of efavirenz after nevirapine-related adverse events. *Clin Infect Dis*, 31 (3), 506-507.
- Department of Health and Human Services. Guidelines available from all AETC offices and at www.hivatis.org
- Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents* (February 4, 2002 [Living Document]).
- Guidelines for the use of antiretroviral agents in pediatric HIV infection* (December 14, 2001 [Living Document]).
- United States Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing HIV-1 transmission in the United States* (February 4, 2002 [Living Document]).
- Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis* (June 29, 2001).
- Management of possible sexual, injecting-drug-use, or other nonoccupational exposure to HIV, including considerations related to antiretroviral therapy* (September 25, 1998).
- 2001 USPHS/IDSA Guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus* (November 28, 2001 [Living Document]).
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