

2004 Edition

A Guide to Primary Care of People with HIV/AIDS

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Dedication

A Guide to Primary Care of People with HIV/AIDS is dedicated to all the men and women working in the Ryan White CARE Act programs. Their commitment and dedication to serving people living with HIV and AIDS makes these programs possible.

Acknowledgments

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Abbreviations

ALT: alanine aminotransferase

anti-HBc: hepatitis B core antibody

ART: antiretroviral therapy, highly active antiretroviral therapy

bid: twice a day

c/mL: copies of virus per mL

DSP: distal symmetrical polyneuropathy

DRESS: drug rash with eosinophilia and systemic symptoms

FTA-ABS: fluorescent treponemal antibody absorption test for syphilis

HAART: highly active antiretroviral therapy (see ART)

INH: isoniazid

HCV: hepatitis C virus

IVIG: intravenous immune globulin

LDL: low-density lipoprotein

LFT: liver function test

MAC: *Mycobacterium avium* complex

nPEP: nonoccupational postexposure prophylaxis

NRTI: nucleoside reverse transcriptase inhibitor, nucleoside

NNRTI: non-nucleoside reverse transcriptase inhibitor

OD: opportunistic disease

OI: opportunistic infection

po: per os, by mouth

PI: protease inhibitor

PPD: purified protein derivative of tuberculin

qd: every day

qhs: every night

qam: every morning

RPR: rapid plasma regain test for syphilis

SSRI: selective serotonin reuptake inhibitor

STD: sexually transmitted disease

STI: sexually transmitted infection

TB: tuberculosis

VDRL: Venereal Disease Research Laboratory serologic test for syphilis

VL: viral load

Glossary of Antiretroviral Drugs

| Generic name | Abbreviation | Trade name | Class |
|------------------------------------|---------------------|-------------------|------------------|
| abacavir | ABC | Ziagen | nucleoside |
| amprenavir | APV | Agenerase | PI |
| atazanavir | ATV | Reyataz | PI |
| delavirdine | DLV | Rescriptor | NNRTI |
| didanosine | ddI | Videx | nucleoside |
| efavirenz | EFV | Sustiva | NNRTI |
| emtricitabine | FTC | Emtriva | nucleoside |
| enfuvirtide | T-20 | Fuzeon | fusion inhibitor |
| fosamprenavir | FPV | Lexiva | PI |
| indinavir | IDV | Crixivan | PI |
| lamivudine | 3TC | Epivir | nucleoside |
| lopinavir + ritonavir | LPV/r | Kaletra | PIs |
| nelfinavir | NFV | Viracept | PI |
| nevirapine | NVP | Viramine | NNRTI |
| ritonavir | RTV | Norvir | PI |
| saquinavir | SQV soft gel cap | Fortovase | PI |
| saquinavir | SQV hard gel cap | Invirase | PI |
| stavudine | d4T | Zerit | nucleoside |
| tenofovir | TDF | Viread | nucleotide |
| zalcitabine | ddC | Hivid | nucleoside |
| zidovudine | AZT, ZDV | Retrovir | nucleoside |
| zidovudine + lamivudine | AZT + 3TC | Combivir | nucleosides |
| zidovudine + lamivudine + abacavir | AZT + 3TC + ABC | Trizivir | nucleosides |

PI: protease inhibitor

NNRTI: non-nucleoside reverse transcriptase inhibitor

nucleoside: nucleoside reverse transcriptase inhibitor
(NRTI)

Chapter 1:

Primary Care as Chronic Care

1

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What is a primary care approach to the treatment of HIV/AIDS, and why is it important?

People with HIV/AIDS can live longer, healthier lives because of advances in treatment of HIV infection. However, longer lives are associated with increased prevalence of 1) adverse effects of HIV infection, 2) adverse effects of the drugs used to treat HIV, and 3) concurrent medical conditions that would occur in the absence of HIV. These long-term complications have put HIV infection in the realm of chronic diseases rather than of infectious diseases, which usually respond to short-term clinical interventions.

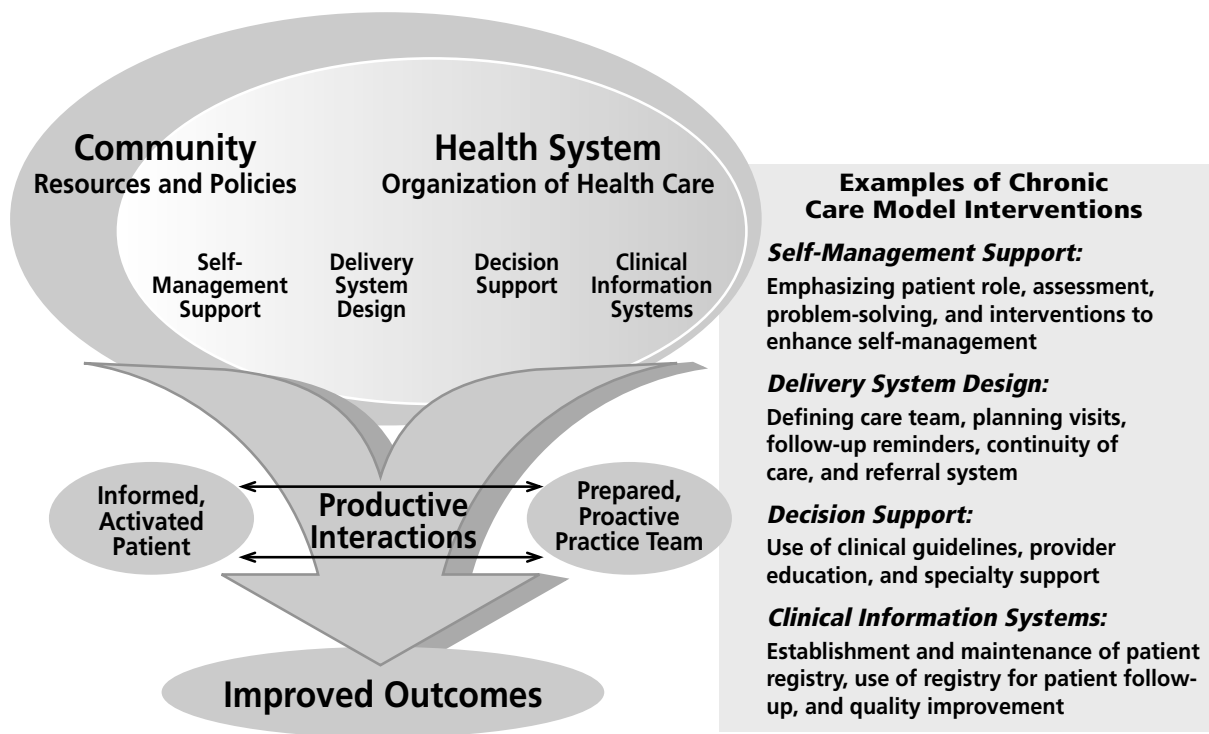
Effective management of chronic diseases in the primary care setting requires the coordination of interventions that occur at the level of the clinical services, the community supports for those clinical services, and the individual patient. While clinical services begin in the primary care clinic, community supports are needed, and the patient must be engaged to enhance self-management. The coordinated interventions together contribute to the desired clinical outcomes. The Chronic Care Model, which is used in the design and quality improvement activities of clinical services, conceptualizes how these factors impact the clinical outcome of chronic disease management (see Figure 1-1).

What is the purpose of this guide?

This book addresses several important aspects of HIV/AIDS care and treatment in a concise, accessible format; it is not meant to be a comprehensive reference book. Recommended references and citations are provided for the reader to be able to access in-depth information on topics that are particularly important and/or controversial. Appropriate use of antiretroviral drugs, treatment of opportunistic infections, symptom management, treatment of concurrent medical conditions, and other specific interventions to treat HIV disease and its complications are addressed.

The format of this guide is designed to provide practical information for the common questions that arise in the care of patients with HIV infection. Recognizing the broader array of best practices that contribute to effective clinical outcomes among patients with a complex array of service needs, the authors also address patient evaluation, adherence, mental health, substance abuse, overall clinic management, and other factors that lead to improved patient outcomes according to the Chronic Care Model. Last, because the authors recognize the challenges of maintaining clinical practices in the face of rapidly changing and ever more complex treatment interventions, a chapter on sources for updated and in-depth clinical information is provided. Pediatric HIV/AIDS treatment is not addressed in this book.

Figure 1-1. The Chronic Care Model



Source: Adapted from Wagner EH. Chronic disease management: What will it take to improve care for chronic illness? *Effective Clinical Practice*. 1998;1:2-4. Reprinted with permission. The Chronic Care Model was developed by Ed Wagner, MD, MPH, Director of the MacColl Institute for Healthcare Innovation, Group Health Cooperative of Puget Sound, and colleagues with support from The Robert Wood Johnson Foundation. Further details can be found at www.ihl.org.

Who is the target audience?

The target audience is providers of primary medical care, such as physicians, physician assistants, and nurse practitioners, who are taking care of a small but perhaps an increasing number of HIV-infected persons but who are not experts in HIV care. Parts of this book will also be useful for nurses, counselors, pharmacists, and others seeking specific, concise information about the treatment of HIV-infected persons. Last, specific chapters on clinic management and quality improvement are relevant for those responsible for the administration of clinical sites treating patients with HIV/AIDS. Clinicians with small numbers of patients with HIV/AIDS are encouraged to seek appropriate expert consultation when complex clinical situations arise. Provider expertise in HIV care is essential in many treatment decisions. In fact, patient outcome is correlated with the number of patients with HIV a provider has treated. For more information, see Suggested Resources in Chapter 18 on Keeping Up-to-Date: Sources of Information for the Practicing Clinician.

What is the purpose of the pocket guide contained within the book?

The guide is a pocket-sized quick reference that provides a summary of all Federal guidelines dealing with HIV, including antiretroviral therapy (ART), prevention of opportunistic infections (OIs), management of class adverse reactions, treatment of tuberculosis (TB) and hepatitis C (HCV), laboratory testing, prevention after occupational exposure, and HIV management in pregnancy. It is presented in a format that is intended for point-of-care decision making: it can be carried in the clinic and at the bedside to rapidly access needed information for patient treatment.

The pocket guide will be updated more frequently than the book to meet rapid changes in HIV medication options and recommendations.

How will the book keep pace with the rapidly changing field of HIV/AIDS treatment?

The book details principles and major recommendations for the treatment of persons with HIV/AIDS that will remain, for the most part, relevant for the coming 2 or 3 years. However, the field of HIV treatment is very fluid, and specific drugs and drug combinations evolve rapidly. For this reason, such information has been consolidated in the pocket guide, which will be revised, with updates available in the on-line version on the HIV/AIDS Bureau (HAB) website. Revisions of the pocket guide will include new drugs, new treatment guidelines, and new side effects as well as new drug interactions. In addition to the pocket guide, information on other useful websites is provided to help with keeping up-to-date.

KEY POINTS

HIV is now a chronic disease requiring ongoing primary care management.

The chronic care model uses coordinated interventions at the clinic, community, and individual levels.

A Guide to Primary Care of People with HIV/AIDS is for primary care providers who are taking care of a small number of patients with HIV but who are not experts in HIV care.

The Pocket Guide provides easy reference to rapidly changing treatment guidelines for point-of-care decision making.

Chapter 2:

Approach to the Patient

John V. L. Sheffield, MD
Gloria A. Casale, MD, MSPH

2

BASIC ELEMENTS OF CARE
STIGMA AND DISCRIMINATION
CONFIDENTIALITY AND DISCLOSURE
PATIENT EDUCATION
RISK ASSESSMENT AND COUNSELING
KEY POINTS
SUGGESTED RESOURCES

BASIC ELEMENTS OF CARE

What are the special challenges of caring for patients with HIV/AIDS?

Providers need to be mindful of several special issues:

- Patients infected with HIV face a complex array of medical, psychological, and social challenges. A strong provider-patient relationship, the assistance of a multidisciplinary care team, and frequent office visits are usually required to provide excellent care.
- The stigma associated with HIV/AIDS places a major psychological burden on patients. Confidentiality is critical, as is a careful assessment of each patient's emotional support system.
- Ethnic minorities are over-represented among people with HIV. Efforts to understand and acknowledge the beliefs of patients from a variety of cultural backgrounds are necessary to establish trust between providers and patients.
- Providers play a key role in the public health system's HIV prevention strategy. Disease reporting, partner notification, and risk assessment are important aspects of care.
- Many patients have inaccurate AIDS information that can heighten their anxiety, sabotaging treatment adherence and appropriate prevention behaviors. They need assurance that HIV is a treatable disease and that with successful treatment, patients may live indefinitely. They also need to hear explicitly that HIV is transmitted through sexual contact, intravenous drug use, and blood contact (perinatal or other) and how they can prevent transmission to others.

What are the important components of good HIV care?

The elements that ensure good care for people with HIV/AIDS include mechanisms for coordination and communication of care:

- Clinics must offer a nonjudgmental and supportive environment because of the sensitive nature of issues that must be discussed.

- A multidisciplinary approach, utilizing the special skills of nurses, pharmacists, nutritionists, social workers, and case managers is highly desirable to help physicians address patients' needs regarding housing, medical insurance, emotional support, financial benefits, substance abuse counseling, and legal issues.
- Providers and other clinic staff should be prepared to conduct appropriate interventions and make timely referrals to community resources and institutions.
- The primary provider should coordinate care, with close communication among providers across disciplines.
- Individual office visits should be long enough to allow a thorough evaluation.
- Providers must be able to see patients frequently for good continuity of care, and clinic scheduling should be flexible so that patients with acute problems can be seen quickly.
- A range of medical resources, including providers with subspecialties and laboratory expertise, must be in place (see Chapter 16: Clinic Management).
- Patient education is a vital aspect of care that begins during the initial evaluation and continues throughout the course of care (see section on Patient Education below).

What steps can providers take to enhance care?

Providing comprehensive care for patients infected with HIV requires a lot of time, attention to detail, and a strong patient-provider relationship. Specifically, the provider should do the following:

- Discuss issues in a straightforward fashion to foster trust and openness.
- Be realistic about the seriousness of HIV disease and yet, to instill hope, be optimistic about the potential to restore health and to provide comfort. Give accurate information regarding prognosis and the real hope that antiretrovirals provide.
- Encourage patients to learn all they can about their condition and take an active role in decisions regarding their care.

- Anticipate that significant time will be required for patient education (see section on Patient Education below).
- Explicitly outline clinic operations and expectations for provider-patient communication.
- Plan to see patients often and communicate regularly between visits to answer questions, assess treatment effectiveness, and manage side effects.
- Arrange to see patients with acute problems quickly.

How can providers help patients with HIV/AIDS cope with the emotional issues they face?

Patients coming to terms with HIV infection often experience a range of emotions, including anger, fear, shock, disbelief, sadness, and depression. Loss is a major issue for patients with HIV disease because health, employment, income, relationships with friends, lovers, and family, and hope may all be threatened. Many patients feel overwhelmed, and providers need to recognize that a patient's emotional state affects the ability to solve problems and attend to important medical or social issues. Even patients who seem to be adjusting reasonably well can find it difficult to keep all of the appointments that are scheduled as they initiate care. Providers can do the following:

- Assess each patient's emotional state and the availability of friends and family for emotional support. Patients may feel hesitant about seeking emotional support, and some will need counseling to help them decide whether to disclose their diagnosis to friends, family, or employers.
- Deliver important information in easily understood terms and in small amounts. Reassess patient understanding of crucial information at subsequent visits, and repeat important information as necessary.
- Screen for anxiety, depression (including suicidal ideation), and substance use.
- Refer patients to community resources for crisis counseling, support groups, and, if appropriate, psychiatric treatment to help them achieve emotional stability (see also Chapter 14: Mental Health Disorders).
- Assign a case manager who can help reduce anxiety about keeping life in order.

STIGMA AND DISCRIMINATION

Why is stigma associated with HIV/AIDS?

Stigma is founded on fear and misinformation. Theodore de Bruyn has observed that stigma is associated with HIV/AIDS because "it is a life-

threatening disease; people are afraid of contracting HIV; it is associated with behaviors that are considered deviant; a belief that HIV/AIDS has been contracted due to unacceptable lifestyle choices; and, some believe it is the result of a moral fault which deserves punishment" (de Bruyn, Theodore. Paper prepared for the Canadian HIV/AIDS Legal Network. 1999).

Stigma can adversely affect how patients are perceived by others and how they view themselves. The stigma associated with HIV/AIDS is such that individuals known to be or suspected of being infected with HIV may be excluded from community activities and suffer isolation or abandonment. Some patients may feel ambivalent about seeking medical care if by doing so they risk disclosing their condition. Others may have learned from experience to expect rejection and are therefore untrusting of all care providers. It is essential for providers to be supportive of patients dealing with the burden of stigma.

How can providers support patients facing the stigma of fear of contagion?

The clinic must be inviting, and *all* staff members must model behavior in this area. For example, gloves should be worn only as appropriate during physical exams and as consistent with universal precautions. There should not be separate facilities or procedures for HIV-infected patients. Patients and their families are often unaware that routine household contact with a person with HIV poses no risk of contagion. They should be educated about this but also taught what to do in situations that do pose risk, such as bleeding.

How can providers support patients who face stigma associated with being gay, lesbian, bisexual, or transgender?

Demonstrating respect and providing excellent care to patients with various cultural backgrounds, beliefs, and sexual orientations define professionalism. Providers should approach patients in an open and nonjudgmental fashion and be familiar with medical management issues unique to these populations, such as STD screening for men who have sex with men (MSM) and high-dose hormonal treatment for transgender male-to-female patients. Clinic staff members must also be respectful and supportive; having staff who are familiar with gay and lesbian culture is a natural way to create a welcoming environment. Providers and social workers should be aware of community agencies with resources available to people who are gay, lesbian, or transgender. In addition, providers and clinic staff should be aware of special legal issues that affect these populations. For

example, designating a durable power of attorney for medical decision making can be particularly important in states that do not recognize same-gender partners as legal next of kin.

What other special cultural issues affect patients infected with HIV?

Minorities are disproportionately affected by HIV, and many people of color with HIV disease have major socioeconomic problems such as poverty, homelessness, lack of medical insurance, lack of acculturation, and undocumented immigration status. All of these can make accessing health care difficult and attending to health problems less of a priority. A patient's cultural background influences health beliefs and behaviors, and the effectiveness of provider-patient communication may affect compliance with therapy. In addition, prior adverse experiences may make some patients distrustful of medical care. For all of these reasons, providers should do the following:

- Carefully explore what each patient believes about his or her health, what would be appropriate treatment, and who should be involved in medical decision making.
- Use professional interpreters to help overcome language barriers.
- Use case managers to help overcome social barriers.

CONFIDENTIALITY AND DISCLOSURE

Why is confidentiality especially important for patients with HIV disease?

Confidentiality of medical information is always mandatory, but the stakes are particularly high for patients infected with HIV, who risk losing medical insurance, employment, or the support of friends or family if the wrong individuals learn of their diagnosis. Unfortunately, fear and ignorance persist regarding HIV transmission; people with HIV disease may be shunned because of the incorrect belief that HIV can be transmitted via casual contact. Although people with HIV disease are protected against discrimination under provisions of the Americans with Disabilities Act, discrimination can be difficult to prove, and there are strict time limits after which charges of discrimination can no longer be made.

What steps should providers take to protect patient confidentiality?

By adhering to the newly implemented Health Insurance Portability and Accountability Act (HIPAA) regulations, providers are protecting patient confidentiality. Personnel policies should reinforce measures such as requiring that papers and computer screens containing patient identifying information not be left unattended and documenting whether phone messages can be left for the patient, and if they can, with whom.

How can providers help patients decide whom to disclose their HIV status to?

Patients with a support network function better than those who are isolated. However, patients' fear of disclosure is often well founded, and providers must find a balance between accepting patients' unwillingness to disclose and the need to develop support networks. Patients may find support groups or individual psychotherapy sessions beneficial in deciding to whom and when to disclose.

The sex and needle-sharing partners of people with HIV need to be informed about their possible exposure to HIV. The local health department should be able to either assist patients in making these disclosures or provide anonymous partner notification for them.

What public health role do providers play in the HIV epidemic?

Primary care providers must also consider their public health role in curbing the spread of HIV. The nationwide increase in the incidence of syphilis and gonorrhea, especially among MSM, suggests that the advent of potent antiretroviral therapy has resulted in relaxed adherence to safer sex recommendations. All patients with a diagnosis of AIDS and, in many states, those with a positive HIV test must be reported to the State health department. Laws vary by state regarding reporting requirements and subsequent notification of potentially exposed individuals, but the name of the source contact is never divulged to the person being notified. Providers should become familiar with the laws of their jurisdiction by contacting their health departments. (The Association of State and Territorial Health Officers provides links to all State health departments at: <http://www.astho.org>.) Providers are required to do the following:

- Inform patients whose positive HIV or AIDS status must be reported to the State health department, tell them if partner notification is required, and explain what they should expect regarding efforts that must be made by the patient, provider, or health department to notify sex partners or individuals who may have been exposed to HIV through their needle sharing. Assure them that the patient's name is always kept confidential, and is never given to potentially exposed individuals by the Health Department.
- Carefully assess patients' risk-taking behaviors, educate them regarding HIV transmission, and perform STD screening (see question on STD screening in this chapter).
- Provide counseling to encourage safer sexual practices (see section on Risk Assessment and Counseling below) and make referrals to drug rehabilitation or needle exchange centers (see Chapter 13: Management of Substance Abuse).
- The importance of adhering completely to the treatment regimen
- The possibility of drug resistance and loss of treatment options
- The proper timing of pills and coordinating pill-taking with meals
- Possible side effects and long-term drug toxicities
- The option to stop treatment at any time

In addition, patients should express a commitment to adhere to treatment before providers initiate any form of treatment. (For more on adherence, see Chapter 7: Adherence.)

The recently released Federal guidelines on prevention for persons living with HIV, which contain recommendations for providers, are listed in the Suggested Resources below. (See also Chapter 4: Prevention of HIV in the Clinical Care Setting.)

PATIENT EDUCATION

What does patient education involve?

The provider should assess the patient's understanding of HIV disease and begin patient education at the initial evaluation. To make sound decisions regarding treatment, the patient must understand certain medical information, including:

- The critical role of the patient in his or her own care
- Natural history of HIV disease and consequences of immune system destruction
- How HIV is transmitted
- The meaning of the viral load and CD4 count
- The beneficial impact of antiretroviral drugs
- Early signs and symptoms of opportunistic illnesses
- The role of prophylactic agents

What should patients understand before beginning antiretroviral therapy?

Before initiating antiretroviral therapy, patients must be fully aware of:

How should providers incorporate patient education into care?

Patient education is so important that entire clinic visits are often devoted to a discussion of key concepts. Providers should use easily understood language and confirm the patient's understanding of medical terms and concepts. During these discussions, it is helpful for providers to be flexible, acknowledging that uncertainties exist regarding optimal medical management of HIV disease.

Because patient education is time-consuming, many HIV specialty clinics utilize staff other than the primary care provider, such as nurses and nurse practitioners who specialize in HIV clinical care, physician's assistants, pharmacists, and trained peer educators. This interdisciplinary team approach can supplement the limited time primary care providers often have with patients.

What information resources are available for patients?

Clinics can provide patient education materials and make referrals to social workers, nutritionists, pharmacists, and financial advisers who serve as first-line sources of information about medical issues and social services available in the community. At the regional level, community-based HIV/AIDS organizations and county and State public health departments offer information about medical care and facilitate access to legal aid, financial assistance, low-income housing, support groups, and other social services. At the national level, many organizations provide comprehensive information about HIV/AIDS. Table 2-1 lists recommended resources to which providers can refer patients for information and support.

| Table 2-1. Information Resources for Patients | | |
|--|--|---|
| Internet Sites | | |
| Agency | Topics | Web address (accessed 4/04) |
| AIDS Education Global Information System | Daily briefing; key topics; basics; fact sheets | http://www.aegis.com |
| AIDS Gateway to the Internet | Fact sheets; conferences; news; community | http://www.aids.org |
| AIDS Info | Resource for federally and privately funded clinical trials | http://www.aidsinfo.nih.gov/ |
| AIDSmeds.com | Extensive treatment information | http://www.aidsmeds.com |
| American Association of Family Practice | Health topics | http://familydoctor.org |
| Centers for Disease Control and Prevention | Health topics; traveler's health | http://www.cdc.gov |
| Guides for Living | Database of social service organizations | http://www.guides4living.com |
| HIV InSite | Comprehensive site for providers and patients | http://hivinsite.ucsf.edu/ |
| Johns Hopkins AIDS Service | Comprehensive site for providers and patients; expert Q & A; resources | http://www.hopkins-aids.edu/ |
| New Mexico AIDS Info | Fact sheets; internet bookmarks | http://www.aidsinonet.org |
| Project Inform | Fact sheets; outreach and education; publications | http://www.projectinform.org |
| San Francisco AIDS Foundation | AIDS 101; treatment; prevention | http://www.sfaf.org |
| The Body | Comprehensive AIDS and HIV information resource | http://www.thebody.com |
| The Well Project | Resource for HIV positive women | http://www.thewellproject.com |
| Phone Numbers | | |
| Agency | Topics | Phone number(s) |
| AIDS Clinical Trials Information Service | Clinical trials information | 1-800-874-2572 |
| CDC National AIDS Hotline | General AIDS information, local resources for HIV testing and services | English 1-800-342-2437 (24/7) Spanish 1-800-344-7432 (8 am - 2 am EST) TTY 1-800-243-7889 |
| Guides for Living | National resource directory | 1-303-702-1254 |
| Social Security Benefits | How to apply for social security benefits | 1-800-772-1213 |
| Project Inform | Treatment information | 1-800-822-7422 |
| AIDS Treatment Information Service | Treatment information | 1-800-448-0440 |
| Direct Access Alternative Information Resources | Alternative Treatments | 1-888-951-5433 NYC: 1-212-725-6994 |

RISK ASSESSMENT AND COUNSELING

What risk-taking behaviors should be reviewed with patients?

Patients infected with HIV who practice unsafe sex or inject drugs can infect others, be reinfected themselves with new HIV strains, or contract STDs, viral hepatitis, or other infections. Abuse of alcohol or illicit drugs is directly harmful and may affect adherence to a complicated medical regimen. Accordingly, providers need a detailed understanding of their patients' risk-taking behaviors to guide patient education and counseling efforts and to assess the advisability of initiating antiretroviral treatment.

Table 2-2 lists specific risk-taking behaviors to review with patients. See also Chapter 4: Prevention of HIV in the Clinical Care Setting and Chapter 13: Management of Substance Abuse.

Table 2-2. Risk-Taking Behaviors to Review with Patients Infected with HIV

Sexual Practices

Number and gender of partners

Specific sexual practices

Frequency

Condom use

HIV status of partners and disclosure of patient's HIV status

Anonymous partners

Association with drug use

Prior STDs

Genital ulcer disease

Drugs

Substances used

Routes of administration

Tolerance and history of withdrawal

History of drug treatment

How should one ask about risk-taking behaviors?

Explaining the rationale for reviewing risk-taking behaviors, informing patients that such a review is routine, and asking for a patient's permission to discuss these topics is a good way to initiate the conversation.

Projecting comfort with the subject material and proceeding in a poised, professional, nonjudgmental, and supportive fashion will engender trust and help patients feel safe enough to discuss their behavior. With regard to sexual behavior, asking "Do you have sex with men, women, or both?" indicates the provider's openness to all sexual orientations. Making a comment that many men who have sex with men, particularly in certain cultures, do not self-identify as gay assures patients that discussing their behavior will not cause the provider to categorize them without their consent. Providers should also explore factors associated with sexual abstinence.

At the same time, it is important for providers to be realistic. Wanting a satisfying sex life is a reasonable desire; the goal is to minimize risk associated with sex. Similarly, changing addictive behavior is extremely difficult and often requires several attempts. Discussing realistic goals will enhance a provider's credibility and minimize a patient's resistance to discussing these subjects. The goal of this initial survey is to learn what patients are doing, not to draw battle lines.

What are effective counseling strategies to help patients decrease their risk taking?

When discussing risk-taking behaviors, a key first goal is to assess a patient's state of preparedness for change. Some patients with newly diagnosed HIV come to care motivated to make healthy lifestyle changes. For these individuals, an enhanced understanding of the risks associated with certain behaviors in conjunction with a provider's strong recommendation to modify behavior may suffice. Providers should also be prepared to offer appropriate medications (e.g., to assist with smoking cessation) or referrals for drug and alcohol abuse counseling. For patients with complicating factors such as severe mental illness, substance abuse, domestic violence, or sexual abuse, referral and close linkages with specialty care are essential.

What if a patient is not prepared to make lifestyle changes?

Providers should deliver a clear, unequivocal message regarding the risks to patients and others associated with unsafe sex and ongoing drug use and advise patients of ways, such as safer sexual practices and needle exchange programs, to reduce risk. It should be kept in mind, however, that pushing patients unprepared for behavioral change may lead to animosity and resistance and that direct advice alone is unlikely to result in immediate or sustained behavioral change. For example, advice to stop smoking generally results in 12-month success rates of 5%-

10%. For patients unprepared to alter their risk-taking behavior, a longer-term strategy is required, and a nonconfrontational approach such as motivational interviewing is recommended (see Table 2-3).

When working with a patient over time to support behavioral change, it is crucial for the provider to be a consistent source of support, hope, and optimism. By acknowledging positive efforts even when initial attempts to modify behavior fail, by continuing to offer encouragement, and by supporting even small progress, the provider can help bolster a patient's resolve and sense of control over his or her actions.

Table 2-3. Motivational Interviewing

Basic Steps:

- Seek to understand the patient's experience through careful and reflective listening.
- Help the patient voice his or her own reasons for change.
- Recognize and accept resistance to change.
- Affirm the patient's ability to control his or her own actions.

In this patient-centered approach, the provider seeks an accurate understanding of the patient's unique experience with certain behaviors. The interviewer listens carefully to the patient's thoughts about his or her behavior, monitors readiness for change, clarifies what the patient believes to be obstacles to change, identifies the patient's own self-motivational statements, and selectively reinforces these expressions of desire, intent, and ability to change. In this manner, the provider yields the role of "expert" and offers affirmation and support for the patient's ability to control his or her own behavior.

Principles to Remember:

- For most people, motivation for change must come from within. Direct persuasion does not often result in sustained behavioral change.
- It is the patient's task to articulate resolve and ambivalence.
- When patients voice resistance to change, it is preferable to recognize and accept a lack of readiness than to press for immediate change. Timing is important.
- Patients must understand that resolutions to change often slip, and failure should not become a reason to avoid contact with the provider.

KEY POINTS

Caring for patients with HIV/AIDS requires a strong provider-patient relationship, a multidisciplinary care team, and frequent office visits.

Stigma and discrimination must be addressed through strong confidentiality protections, emotional support, and cultural sensitivity.

Patient education about the disease process, treatment, and community resources is a vital component of care.

The primary care provider plays a key role in risk assessment and counseling for all patients with HIV.



SUGGESTED RESOURCES

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Centers for Disease Control and Prevention. Incorporating HIV prevention into the medical care of persons living with HIV. *MMWR Recommendations and Reports*, (July 18, 2003; 52(RR12);1-24.

Hecht FM, Wilson IB, Wu AW, Cook RL, Turner BJ. Society of General Internal Medicine AIDS Task Force. Optimizing care for persons with HIV infection. *Ann Intern Med*. 1999;131:136-143.

Positive Living. A practical guide for people with HIV. Seattle: Public Health–Seattle & King County, HIV/AIDS Program; 1999.

Rollnick S, Miller WR. What is motivational interviewing? *Behavioral and Cognitive Psychotherapy*. 1995;23:325-334.

Chapter 3:

Core Elements of HIV Primary Care

*John McNeil, MD
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*INITIAL EVALUATION
ONGOING CARE
KEY POINTS
SUGGESTED RESOURCES*

3

INITIAL EVALUATION

What are the goals of the initial evaluation?

The goals will depend to a large extent on why the patient is being seen by the primary care provider, which may be because of symptoms, the need for evaluation after a positive HIV test, referral, for a consultation, etc. The initial evaluation should be tailored to the patient's specific need, but the following are the usual goals of the initial evaluation:

- Evaluate HIV-related complaints that require immediate intervention
- Establish a strong patient-provider relationship with clear lines of communication
- Initiate a complete medical database (Table 3-1)
- Assess the patient's understanding of HIV disease
- Identify health needs for current medical problems, including those associated with mental health, substance abuse, hepatitis, and hypertension
- Assess the need for social and psychological intervention
- Assess the need for consultants for medical, social, or psychiatric care
- Describe HIV disease in lay terms, including natural history, laboratory tests (CD4 cell count and viral load), complications, treatment, and outcome
- Describe methods of transmission and of prevention

This is a large menu, and there may need to be several "first visits."

What are the important aspects of the initial evaluation in patients with symptoms?

It is critical to learn quickly if the patient has any HIV-related complications that indicate advanced disease and may require rapid intervention. The most common presentations related to earlier HIV disease are thrush, weight loss, skin lesions of Kaposi's sarcoma, *Pneumocystis carinii* pneumonia (PCP), and fever. Patients with HIV can also have medical conditions that stem from other causes, such as headaches, upper respiratory infections (URI), gastroesophageal reflux disease (GERD), hypertension, diabetes, or heart disease. Distinction between these and conditions that are HIV-related may be obvious, but when not, the best laboratory test is a CD4 cell count, which represents the barometer of immune function with HIV infection. Nearly all HIV-related complications occur when the CD4 cell count is $< 200/\text{mm}^3$. It may take 2-3 days for the laboratory to report the CD4 cell count, but clues to late-stage disease include evidence of chronic illness with weight loss and/or fever, and/or a total lymphocyte count of $< 1,000/\text{mL}$ which is readily available from a stat complete blood count (WBC x % lymphocytes). Late-stage HIV also is an indication of some urgency to initiate antiretroviral therapy. Some patients present with late complications such as PCP, cryptococcal meningitis, toxoplasmosis, or cytomegalovirus (CMV) retinitis. When these are in the differential diagnosis, the workup may require hospitalization, consultation, extensive testing, and frequent followup by telephone or clinic visit. These are medical emergencies – all are ultimately lethal and all are treatable.

Table 3-1. Initial History and Physical Examination: Key Areas for Patients with HIV/AIDS

| History | |
|-------------------------------------|--|
| Emotional reaction to HIV diagnosis | Availability of friends and family for support |
| HIV-specific information | First known positive HIV test Documentation of positive HIV test Possible timing and risk factors for HIV infection Opportunistic illnesses Prior CD4 counts, viral load measurements, and resistance tests Prior antiretroviral therapy and side effects Understanding of HIV disease Transmission, natural history of immune-response destruction and opportunistic infections, significance of CD4 counts and viral load, and antiretroviral therapy |
| Risk assessment | Risk category Sexual behavior history (see Table 2-2) Current sexual activity History of syphilis and other STDs Substance abuse history Intravenous and other substance abuse Rehabilitation and interest in rehabilitation |
| Past medical history | Use of alternative medicine Mental health history Reproductive history, including pregnancies since becoming HIV positive, and plans for pregnancy Tuberculosis history History of positive PPD test, TB disease, or treatment of latent TB infection Concurrent medical conditions (diabetes, coronary artery disease, hypertension, etc.) Hospitalizations |
| Social history | Housing Food sources, 3-day diet history Income, employment, and insurance Emergency contacts Legal issues Living will and durable power of attorney for medical decisions Permanency planning for dependent children |
| Physical Examination | |
| Vital signs, weight, height | |
| Skin | Dermatitis, folliculitis, fungal infections, molluscum, and Kaposi sarcoma |
| HEENT | Retinal exam (with CD4 < 200/mm ³) Oropharynx: oral hairy leukoplakia, candidiasis, dentition |
| Lymph nodes | Cervical, axillary, inguinal |
| Abdomen | Liver and spleen |
| Neurologic status | Special focus on mental status and sensation |
| Genital and rectal findings | Discharges, ulcers, and warts |

What are important aspects of the initial history in asymptomatic patients?

The encounters should be tailored to the idiosyncrasies of the individual patient's needs supplemented with the collection of some routine information about their HIV and general health status. The patient's most pressing concern may require confirming the diagnosis, addressing denial, dealing with "HIV hysteria," evaluating conditions unrelated to HIV, or evaluating for antiretroviral therapy (ART). For patients with prior medical treatment for HIV infection, the previous records are often critical for efficiency in time and cost. When possible, these should be brought by the patient or sent in advance of the visit. The type of information that is particularly useful is the record of CD4 cell counts and viral loads, HIV-related complications, current and prior medications, including information about tolerance, toxicity, and adherence (see Table 3-1).

What information do patients need to know about HIV?

HIV is a chronic infection, which will be lifelong, and its outcome will depend to a large extent on the patient's understanding of the disease process and management. Parallels with type 1 diabetes are clear. With this in mind, it is very important that the patient have access to information to advance his or her understanding of the disease. Essential knowledge includes:

- **Transmission** Sex, injection drug use, and perinatal transmission are the "big 3" and have accounted for virtually all cases in the United States since blood began being screened in 1985.
- **Natural history** Explain the 5 stages: 1) acute HIV, 2) seroconversion, 3) long period with no symptoms and decreasing CD4 cell count, 4) complications when the CD4 cell count is $<200/\text{mm}^3$, and 5) lethal outcome. Emphasize that without therapy the average untreated patient survives about 10 years from HIV acquisition to death, but there is a great deal of individual variation.
- **What does the CD4 cell count mean?** This is the cell that becomes infected with HIV, it is also the quarterback of the immune system, and the count is a barometer of immunosuppression. Normal is $>500/\text{mm}^3$; a count of $<200/\text{mm}^3$ is the definition of AIDS.
- **What does the viral load mean?** This indicates the amount of HIV in the blood. The average is about 30,000 copies per ml (c/ml), but again there is a great deal of individual variation. When it is high, the CD4 cell count tends to decline rapidly (negative CD4 slope). The goal of therapy is to reduce the viral load to undetectable levels, and with this the CD4 cell count usually increases 100-150 cells/ mm^3 each year.

- **Therapy** Potent antiretroviral therapy (ART, also called highly active antiretroviral therapy, or HAART) has revolutionized the course of this disease. Although a miraculous development, HAART is also terribly demanding for the patient in terms of adherence, and some patients have big problems with side effects that are either short-term (eg, nausea, rash, asthenia) or long-term (eg, fat redistribution, hyperlipidemia, peripheral neuropathy). The benefits clearly outweigh the risks, and HIV is no longer an inevitably progressive disease, but is a chronic condition such as hypertension or diabetes that requires continual observation and care.
- **Cure** No cure yet and unlikely to be with any of the current medications.
- **Prevention** See discussion below.

For more information, see Chapter 2: Approach to the Patient (section on Patient Education, especially Table 2-1, Information Resources for Patients).

How should prevention be addressed?

Prevention needs to be addressed early and frequently, usually at every encounter. Nearly all adults who acquired HIV after 1985 did so by sexual exposure or needle sharing in the context of injection drug use. Patients in HIV clinics now constitute an important source for HIV transmission by the same mechanisms. Health care providers are now considered essential in risk reduction with a 3-part responsibility:

- **Risk behavior screening** Patients need to be screened for risk behaviors. The screening includes a history of sexual practices and a clinical assessment for evidence of sexually transmitted diseases (STDs). The history of sexual practices can be taken before patients are seen by the primary care provider, either by another staff member or by having patients complete questionnaires. A component of the assessment includes evaluation for STDs because having STDs is associated with a 5-fold increase in the risk of transmitting HIV and also indicates high-risk sexual activities. Women under 25 years old should be screened for cervical *Chlamydia trachomatis*, all symptomatic patients should be evaluated for gonococcal and chlamydia infection, and asymptomatic patients should be considered for screening for these pathogens. Screening is now facilitated by the use of urine specimens for nucleic acid amplification tests (NAAT) for both *N. gonorrhoeae* and *C. trachomatis*.
- **Risk reduction counseling** The second component of prevention is risk reduction counseling, which may be done in the office or through referral. It is critical that patients be fully informed about how HIV is and is not transmitted and that they be counseled about how they can reduce the risk of transmitting HIV to others.

- **Partner referral** The third component, partner referral, involves asking patients to identify persons whom they have placed at risk through sexual or drug-using behaviors. These persons are then referred to a “Partner Counseling and Referral Service” (PCRS) without identifying the source of the information. The PCRS provides public health resources for confidentially informing partners that they have been exposed to HIV and need HIV counseling and testing.

For more information on prevention, see Chapter 2: Approach to the Patient (section on Risk Assessment and Counseling), Chapter 4: Prevention of HIV in the Clinical Care Setting, and Chapter 13: Management of Substance Abuse .

What are common patient questions?

Patients have many questions when they are newly diagnosed with HIV.

- **What will happen to me?** Patients need to know the facts of HIV regarding prognosis, but emphasis should be placed on the extraordinary benefits of therapy, which, for many, may mean a normal lifespan.
- **Can HIV be cured?** Not with current drugs (but it can be contained).
- **Will I need to take medicine forever?** Patients who respond well to therapy will probably be able to discontinue treatment periodically, but regularly scheduled treatment interruptions generally result in poor long-term control of HIV.
- **Would alternative medicine help me?** Probably not, but some patients seem to think it does. Patients should be encouraged to report any alternative medicines they are taking because some of them are problematic in combination with ART.
- **Will I give HIV to the people I live with?** Patients can give HIV to anyone they have sex with or share needles with; however, they also need to understand that people who live in the same household without that kind of contact are not at risk. It is probably best for people with HIV to have their own toothbrushes and razors and not to share eating utensils that have not been washed, even though HIV is not generally transmitted that way.
- **Are pets a problem for me?** Pets don’t give or get HIV. Occasionally cats will become the source of *Toxoplasma gondii* or *Bartonella*, but this is rare; patients should wash their hands after handling pets and especially before eating, avoid contact with cat stool to prevent toxoplasmosis, and avoid cat bites and scratches and fleas to avoid bartonellosis.
- **Should I have a special diet?** Nutrition is important, but there is nothing idiosyncratic about the needs of people with HIV (see Table 2-1 in Chapter 2 for nutrition resources). With late-stage disease, it might be smart to avoid ingesting lake water because of *Cryptosporidium parvum*, which is commonly present and can cause chronic disease.
- **Can I travel?** Certain vaccines required for travel to developing countries are best avoided by people with suppressed immune systems, but vaccines rarely interfere with travel. The biggest problem may be access to good health care and the usual conditions such as traveler’s diarrhea that can affect any traveler.
- **What will happen if I am around someone with a cold or some other common infection?** This type of exposure would probably cause nothing more than an ordinary cold. People with HIV infection do not become susceptible to infectious complications until the CD4 cell count is low. Then they become vulnerable to a very specific menu of infectious disease complications that are extremely rare in the general public. The infections that are common, such as upper respiratory infections or gastroenteritis, are generally no worse in a person with advanced HIV disease than in a healthy person.
- **My cousin has a newborn infant that I want to visit. Is this a good idea?** There should be no reservations here and no reason to talk about HIV infection. It’s okay to hold, kiss, and hug the child; patients should just obey the simple rules of hygiene that they would under ordinary circumstances.
- **Who should I tell?** People who have been placed at risk either sexually or through drug use need to know, and either the patient can tell them or health department staff can do it. The reason is that they need to be tested so that if they are infected they do not transmit HIV to others, and they also need to gain access to care, which is critical. Beyond that, patients should be counseled to be very careful who they tell about the diagnosis.
- **Do I need to tell people at work?** Generally no. HIV is not transmitted by HIV-infected workers in the work place. A rare exception is some health care workers who could conceivably transmit HIV infection during surgery. Most institutions have policies about health care workers who perform invasive procedures, and these need to be followed. Otherwise, there are no other circumstances in which anyone needs to know unless the symptoms of HIV interfere with effective performance.

What should be covered in the physical exam?

Everything, but special attention should be paid to scrutiny of the vital signs, enlargement of lymph nodes, skin lesions, enlargement of liver or spleen, and mental status (see Table 3-1).

What are the initial laboratory tests to order?

Standard laboratory testing should be done to stage the HIV disease, determine the general health status, and identify the presence of concurrent conditions, and baseline tests should be done on patients who are candidates for ART (see Table 3-2). In general, the CD4 cell count identifies the need to treat with antiretroviral drugs, and the viral load is the major indicator of therapeutic response.

| Table 3-2 Laboratory Testing in HIV Primary Care | | | |
|--|--|---|---|
| (Revised 10/8) | | | |
| Test | Baseline | Repeat | Comment |
| Confirmation of Positive HIV Status | | | |
| Standard HIV serologic test | Either copy of prior lab results or new tests | | Make sure there is a confirmed positive result with standard HIV serologic test |
| HIV Staging | | | |
| CBC | Yes | Repeat at 3-6 month intervals | Repeat more often with some drugs or abnormalities |
| CD4 count | Yes | Repeat at 3-6 month intervals | Evaluates immune status |
| HIV viral load | Yes | Repeat at 3-month intervals | Prognostic indicator Repeat more frequently with initiation of ART |
| Health Status Evaluation | | | |
| Chemistry panel | Yes | Repeat annually | Repeat more frequently with abnormalities |
| Pap smear | Yes | Repeat at 6 months and then annually | |
| PPD | Yes if no history of TB or a prior positive test | Repeat if initial test was negative and patient was exposed, or if CD4 count increased to > 200/mm ³ | |
| Hepatitis screen | | | |
| HAV | Optional | | Screen once to identify candidates for HAV vaccine |
| HBsAg | | | Test if abnormal liver function tests |
| anti-HBc or anti-HBs | Yes | | Identify candidates for HBV vaccine |
| HCV | Yes | | Screen especially if liver disease present |
| STDs | | | |
| VDRL or RPR | Yes | Repeat annually in sexually active patients | Syphilis screen |
| Urine nucleic acid amplification test (NAAT) for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> | Consider for sexually active patients | Consider annual testing or more frequently if at high risk | First-catch urine or urethral (male)/cervical (female) specimen |
| Chest x-ray | Optional | | Must do if positive PPD or chest symptoms |
| <i>Toxoplasma gondii</i> IgG | Yes | | Consider repeating if there are typical symptoms and negative prior test |
| Baseline for HAART | | | |
| Fasting glucose | Yes | | |
| Fasting lipids | Yes | | |

ONGOING CARE

After the initial evaluation is completed, how often do patients need to be seen?

In general, patients with early-stage disease are seen at 3-month intervals to undergo routine medical evaluation and monitoring of CD4 cell count, viral load, and CBC. During the initial evaluation more frequent visits are common because there is so much information to transmit. Visits should also be more frequent when therapy is introduced and when the CD4 cell count is $< 200/\text{mm}^3$ because complications are more likely. It is very important for the primary care provider to thoroughly understand HIV and its complications. In general, the patients are in 4 categories with some overlap: 1) those with a CD4 cell count of $> 200/\text{mm}^3$, whose complaints are rarely due to HIV or its complications, 2) patients with a CD4 cell count of $< 200/\text{mm}^3$, whose new complaints usually reflect an HIV-related complication which is usually both potentially serious and treatable, 3) patients from either group who are receiving ART and other medications, in which case the side effects of the drugs must be considered, and 4) patients with other medical problems, which is actually the rule rather than the exception because of the high frequency of concurrent conditions.

How can one provider take care of all of the problems?

HIV is generally a complex disease in patients with complicated lives, lifestyles, and concurrent conditions. They are best served by a multidisciplinary team with ancillary services for support regarding case management, mental health, substance abuse treatment, transportation, and housing assistance, using the chronic disease model of care. Another model of care emphasizes patient self-management, with the patient as the principal caregiver supported by a well-prepared practice team with a clear division of labor. The patient is linked not only to the provider unit (the clinic) but also to community-based resources and support from the larger health care organization.

What needs to be done in the follow-up evaluations?

Follow-up evaluations are important to document disease trends and response to therapy and to assess high-risk behavior. This includes history, physical exam, and lab tests (see Tables 3-1 and 3-2). In general, the review needs to be tailored to the specific needs of the patient. Sometimes the major issue is a concurrent condition such as hepatitis C, mental illness, or substance abuse requiring resources that are best achieved with a multidisciplinary approach. For patients who are receiving ART and prophylactic drugs to prevent opportunistic infections, heavy emphasis needs to be placed on adherence and drug-related toxicities as discussed in Chapter 7 or on symptoms related to HIV complications as discussed in Chapters 8, 9, and 10. Under all circumstances, it is important to periodically assess the patient's knowledge of HIV since misconceptions are common and patients are often reluctant to ask the questions that bother them most. In virtually all encounters, it is important to emphasize prevention.

In patients at highest risk for STDs (multiple or anonymous partners, sex in conjunction with illicit drug use, patients whose partners participate in these activities, high prevalence of STDs in the area or in the patient population), STD screening is recommended more frequently than annually (see Chapter 4).

KEY POINTS

The focus of the first visit is determined by the patient's most immediate needs.

The initial evaluation is complex and usually requires several visits.

An important aspect of primary care is answering the patient's questions to ensure that he or she understands the HIV disease process and treatment.

While patients with early-stage HIV disease can be seen at 3-month intervals for routine medical evaluation, those receiving ART or with more advanced disease must be seen more frequently.

A multidisciplinary team approach with the patient as primary caregiver is the best approach to care.



SUGGESTED RESOURCES

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WEBSITES

AIDSInfo: <http://www.aidsinfo.com>
Accessed 9/03.

AIDS Education Global Information System:
<http://www.aegis.com> Accessed 9/03.

Centers for Disease Control and Prevention
Division of HIV/AIDS Prevention: <http://www.cdc.gov/hiv/dhap.htm> Accessed 10/03.

HIVInsite: <http://www.hivinsite.ucsf.edu>
Accessed 10/03.

Johns Hopkins AIDS Service: <http://www.hopkins-aids.edu> Accessed 10/03.

STD/HIV Prevention Training Centers: <http://depts.washington.edu/nnptc/> Accessed 10/03.

Chapter 4:

Prevention of HIV in the Clinical Care Setting

Michael P. Johnson, MD, MPH

RATIONALE FOR HIV PREVENTION IN PRIMARY CARE

INTERVENTIONS FOR HIV PREVENTION

KEY POINTS

SUGGESTED RESOURCES

REFERENCES

4

RATIONALE FOR HIV PREVENTION IN PRIMARY CARE

Why is HIV prevention important in the HIV clinical care setting?

Why rob banks?...

Because that is where the money is!

There is growing awareness that the majority of people living with HIV are having sex and that active substance abuse, often with needle-sharing behavior, remains common in the setting of HIV infection (see Chapter 13: Management of Substance Abuse). The HIV clinical care setting provides an opportunity to work with patients to reduce their risk of transmitting HIV to others. Studies are under way to measure the effectiveness of comprehensive clinical care in preventing the spread of HIV. Until those results are available, one should assume that interventions to reduce HIV concentrations in the body through antiretroviral therapy (ART) combined with behavioral counseling to reduce high-risk sexual behaviors and, when indicated, drug abuse treatment are important approaches to decreasing the incidence of HIV infection.

Do most primary care providers incorporate HIV prevention into their care?

Experienced providers, and even HIV specialists, often do not conduct screening and assessment of behavioral risk or offer prevention counseling for their HIV-infected patients. The degree to which these are neglected is startling. Nationwide, approximately a third of HIV-infected patients report that their providers have never counseled them about HIV prevention; in some settings as many as three quarters of HIV medical care providers do not ask about sexual behavior and as many as half do not ask about drug use (Marks et al, 2002; Natter et al,

2002). Results of an unpublished study suggest that HIV specialists are less likely than primary care physicians to engage clients in discussions about sexual and drug-using behaviors. Barriers of time, training, and comfort level contribute to this missed opportunity for HIV prevention.

What factors are associated with high-risk behaviors of people living with HIV?

People living with HIV often practice high-risk sexual and drug-using behaviors in association with poor adherence to clinical care in general and to ART regimens in particular (Wilson et al, 2002). This is of particular concern given the risk of viral resistance with poor medication adherence, which may subsequently result in transmission of resistant viral strains to others. Also, both adherence to HIV prevention practices and adherence to medication regimens appear to be related to mental health problems, which are common among people with HIV (Kalichman et al, 2002). In particular, depression and anxiety disorders are common and should be assessed in patients who report continued high-risk sexual and drug-using behaviors. Any of these conditions should alert the provider to probe for problems in the other conditions or behaviors; addressing underlying issues can lead to improvements in several important behaviors.

What behavioral interventions work to prevent people living with HIV from transmitting HIV?

The earliest behavioral interventions provided factual information and generated fear of AIDS to motivate people to reduce high-risk behavior. Most experts now agree that these interventions do not effectively reduce high-risk behaviors of persons at greatest risk for acquiring HIV, and that generating fear of AIDS most likely increases stigmatization of people living with HIV infection.

A number of counseling interventions have been found to be more effective than providing knowledge alone. Among these effective approaches are brief, provider-delivered counseling messages, which can be delivered within the context of a clinical encounter (Kamb et al, 1998; CDC, 2001). Several theoretical behavioral models have been used to guide counseling interventions. Some common elements of these theory-based counseling approaches include:

- Establishing dialogue and rapport with the client and providing ongoing services in an understanding and nonjudgmental manner, often with the support of trained peers to supplement the provider-based counseling
- Understanding and addressing client needs, situations, and pressures for sexual and drug-using behavior (eg, mental health needs), with emphasis on issues that might be perceived by the client as more pressing than HIV prevention (eg, food, housing, employment), and external barriers to the adoption of safer behaviors (eg, domestic violence)
- Addressing the client's high-risk behavior in a step-wise manner, understanding the readiness and motivation for a change in each specific high-risk behavior, and building the client skills for implementing such changes

These elements are the basis for the assessment and counseling recommendations discussed below, which can be implemented in the clinical setting, along with planning and mobilization of supportive services.

What is the role of drug abuse treatment in preventing HIV transmission?

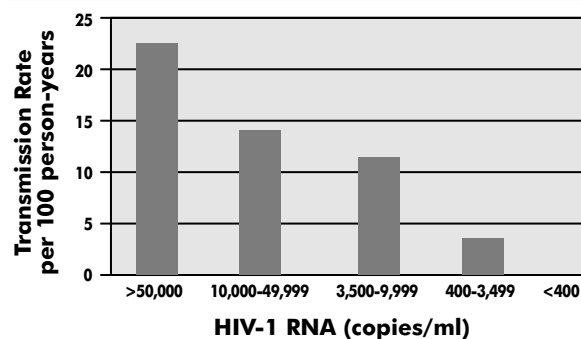
Sharing of drug-injection paraphernalia is directly related to HIV transmission through the transmission of infected blood. Drug and/or alcohol abuse indirectly lead to HIV transmission through the exchange of sex for drugs and enhanced sexual risktaking under the influence of these substances. Drug abuse treatment is an important intervention in the setting of HIV clinical care (see Chapter 13) and should be considered as an important and effective means of HIV prevention among persons with HIV who abuse drugs and/or alcohol.

What is known about the role of antiretroviral therapy in preventing HIV transmission?

Effective ART leads to a decline in plasma viral load, which reduces the risk of maternal-infant HIV transmission. The risk of sexual transmission of HIV is strongly correlated with plasma HIV levels (Quinn, 2000) (see Figure 4-1). There is also a strong correlation between changes in plasma viral load and the HIV

viral load in genital secretions (Ball et al, 1999); however, HIV can be present in genital secretions when plasma HIV is suppressed below the level of detection. While it is highly likely that effective ART leads to a significant reduction in HIV infectivity, from a behavioral standpoint an increase in high-risk sexual behavior because of a sense of lower risk to others has been observed in persons being treated with ART (Dukers, 2001; Scheer, 2001). For this reason, HIV prevention counseling remains important for those on effective ART, and it is particularly important when viral loads rise, eg, due to interruption of therapy and/or emergence of viral resistance.

Figure 4-1. Associations of HIV Plasma Viral Load and Sexual Transmission of HIV



Source: Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med.* 2000;342:921-929. Copyright 2000 Massachusetts Medical Society. All rights reserved. Reprinted with permission.

What is the role of nonoccupational postexposure prophylaxis (nPEP) in the prevention of HIV infection?

Nonoccupational postexposure prophylaxis (nPEP) refers to the use of ART to prevent HIV after a significant sexual exposure to HIV (eg, after sexual assault or condom breakage during intercourse between a discordant couple). A complete review of postexposure prophylaxis (PEP) can be found in Chapter 11: Postexposure Prophylaxis. In summary, a 28-day course of ART may be considered for prevention of nonoccupational HIV transmission if therapy is initiated within 72 hours after a significant exposure from a person with known or suspected HIV infection. This approach will be addressed in upcoming US Public Health Service (PHS) guidelines for nPEP (watch the AIDSInfo website listed in Suggested Resources for these guidelines).

INTERVENTIONS FOR HIV PREVENTION

What can the provider do to enhance prevention practice in the clinical setting?

Primary care interventions to assess and reduce the risk that HIV-infected persons will transmit the virus to others can be conducted at the level of 1) medical care, 2) other care (eg, case management, social services), and 3) clinic structure. Ideally, interventions at all 3 levels are combined to maximize the opportunities for HIV prevention, and each clinic will structure its interventions differently according to its configuration and resources. The following recommendations are directed primarily to the medical provider, although there are often other clinic staff members who support and reinforce these risk assessment and counseling interventions. Training can enhance the skills and motivation for providers to integrate these activities into their routine practice (see Suggested Resources and Chapter 18: Keeping Up-to-Date: Sources of Information for the Provider).

How can the provider identify a patient's risk behaviors?

A brief history should be taken at each regularly scheduled clinic visit to identify knowledge of HIV transmission, sexual and drug-using behavior, and symptoms of an STD (eg, urethral or vaginal burning or discharge, dysuria, genital or anal ulcers, inter-menstrual bleeding, or lower abdominal pain in women). History-taking methods include written, audio, and computerized questionnaires and face-to-face interviews, using either structured or open-ended questions (see examples in Table 4-1). Studies suggest that patients may provide more honest and detailed responses to questionnaires not administered face-to-face. Also, physicians trained in discussing sensitive sexual and drug-using issues are likely to perform better than those who are not. Providers should give positive reinforcement to patients when the screening questions indicate no high-risk sexual and drug-using behaviors. Conversely, indications of high-risk behavior should trigger a medical/laboratory evaluation for STDs, behavioral risk assessment and counseling interventions, and referral and contact notification, as indicated. For more detailed discussion, see the section on Risk Assessment and Counseling in Chapter 2: Approach to the Patient as well as the screening questions for drug abuse in Chapter 13: Management of Substance Abuse.

Table 4-1. Examples of Open- and Closed-ended Risk-screening Questions

Open-ended questions

What do you know about HIV transmission?

What, if anything, are you doing that could result in transmitting HIV to another person?

Tell me about any sexual activity since your last clinic visit.

What do you know about the HIV status of each sex partner?

Tell me about condom use during any sexual activity.

Tell me about any drug use or needle sharing since your last clinic visit.

Closed-ended questions

Do you know the facts about how HIV is and is not transmitted?

Have you had sex (vaginal, anal, or oral) with any partner since your last clinic visit?

For each of your partners, do you know if he/she has HIV infection, doesn't have HIV infection, or are you not sure?

Did you use a condom every time, from start to finish of each sexual encounter?

Have you shared drug injection equipment (including needle, syringe, cotton, cooker, water) with anyone?

Note: Symptoms of STDs (eg, urethral or vaginal burning or discharge, dysuria, genital or anal ulcers, inter-menstrual bleeding or lower abdominal pain among women) are asked in a closed-ended format, regardless of behavioral question format.

What medical and laboratory screening should be done?

Symptoms or signs of an STD or known exposure to STDs should prompt immediate physical and laboratory examinations. However, because STDs are often present without symptoms, every patient should be screened for laboratory evidence of syphilis, trichomonads (women only), gonorrhea, and chlamydia at the initial visit and at least annually (see Table 4-2). Some experts also recommend type-specific testing for herpes simplex virus type 2 because of its association with a higher risk of HIV transmission and possible need

for enhanced counseling. More frequent screening for STDs is appropriate with evidence or suspicion of high-risk sexual behavior (eg, sex with a new partner, sexual activity without consistent and correct condom use); however, there are no data to guide the precise frequency. More frequent screening might also be appropriate in asymptomatic men who have sex with men (MSM) and younger women because of a higher STD prevalence among these demographic groups. The local prevalence of these infections might guide frequency of screening. Laboratory screening for drug abuse is addressed in Chapter 13.

Table 4-2. Screening for Sexually Transmitted Diseases

| STD | Recommended test |
|----------------------|---|
| Syphilis | Non-treponemal serologic test (RPR, VDRL) |
| Gonorrhea | Nucleic acid amplification test (first-catch urine or urethral [male]/cervical [female] specimen) or culture (urethral [male]/cervical [female] specimen) |
| Chlamydia | Nucleic acid amplification test (first-catch urine or urethral [male]/cervical [female] specimen) |
| Trichomonas | Wet mount or culture (vaginal secretion) |
| Herpes simplex virus | Type-specific HSV-2 antibody testing |

What behavioral assessment and counseling interventions should the provider implement?

Specific suggestions for assessment and counseling are presented in Table 4-3 and in Chapter 2. Each clinic must decide which aspects of HIV prevention assessment and counseling are best done by the primary provider, by other clinical providers with whom the patient interacts, or some combination of both. Brief interventions by physicians have been found to be effective with other conditions, including smoking cessation, improving dietary behavior, and reduction of alcohol consumption. Thus, while data are limited on the topic of HIV prevention, physicians should provide such counseling until studies suggest alternate and improved approaches.

How can clinic staff other than the primary medical provider enhance HIV prevention practice?

In most medium-sized and larger clinics, staff members other than the primary medical provider are responsible for referral, contact notification, and quality improvement, which can all be used to enhance prevention practice, as discussed below. In addition, specific structural interventions (eg, arranging client flow to ensure interaction with clinic staff who conduct prevention counseling, use of video, written handouts or other educational media, and distribution of condoms) can strengthen the role of other clinic staff in prevention activities.

What role does referral to community resources play in HIV prevention?

Some complex patient issues and conditions fall beyond the scope of a primary care clinic and must be addressed before risky behavior can be reduced or eliminated. These include drug abuse, mental health issues, domestic violence, and assistance with needs such as housing, food, and employment. Each clinic should have established relationships with community resources to address these issues, and staff members should have thorough knowledge of the available services as well as mechanisms in place to ensure that patients can access the services. Finally, followup should be done to be certain that the referrals are utilized and are effective for each patient. It is unlikely that persons at highest risk for transmitting HIV to others can effectively reduce such behavior without access to a comprehensive array of services and supports.

What are key elements of contact notification?

Contact notification is an effective way to identify additional HIV-infected persons through HIV counseling and testing, bring them into care, and provide support to help them avoid transmitting HIV to others. Health departments traditionally conduct contact notification; in some States providers are required by law to report to the health department known sexual or drug-equipment-sharing contacts of persons infected with HIV. The standard method is to inform the patient’s contacts that they have been placed at risk and need HIV testing without identifying the source.

| Table 4-3. Suggested Counseling Content for Behavioral Risk Reduction | |
|--|--|
| Factual topics about HIV transmission | Suggested content |
| Relative risk of HIV transmission during sex | Most to least risky activities: receptive anal > receptive vaginal > insertive anal > insertive vaginal > receptive oral > insertive oral |
| Preventing HIV transmission during sexual activity | Abstinence (safest behavior) Correct condom use (latex or polyurethane condoms, used with water-based, not oil-based, lubricants, used from start to finish of any sexual penetration) Other means of reducing risk |
| Effect of drug use on sexual decisionmaking | Potential increase in sexual risk behavior following drug and/or alcohol use |
| Risk of HIV transmission when sharing drug-injection equipment | Highest risk for HIV transmission Risk of other disease transmission for either user Entire works (drug paraphernalia), not only needles, need to be clean |
| Impact of viral load level on HIV transmission risk | Greatest risk of HIV transmission when viral load is elevated (eg, when antiretroviral therapy is stopped or is ineffective) HIV transmission still possible during effective antiretroviral therapy (eg, there can be HIV in genital secretions even when plasma viral load is undetectable) |
| Components of assessment and counseling | Suggested content |
| Motivation for HIV prevention | Risk to self: acquiring non-HIV infectious agent and acquiring drug-resistant HIV strain Risk to others: transmitting HIV |
| Readiness and capacity for HIV prevention | Patient's belief about his/her desire, intent, and sense of capacity to adopt behaviors that prevent HIV transmission |
| Barriers to adopting safer sexual and drug-using behaviors | Identification of barriers, such as mental health needs, substance abuse, domestic violence, and other social and economic pressures that might impede the adoption of behaviors to prevent the transmission of HIV |
| Willingness to accept in-depth counseling and/or referral to overcome barriers to adopting safer behaviors | Identification of history of past efforts to address the issue impeding the adoption of safer behavior Encouragement and offering of assistance for more in-depth support through referral |
| Development of an HIV prevention plan | Creation of a plan mutually agreeable to patient and provider, written for both the medical record and the client |
| Discussion of reproductive intentions | Assessment of need for in-depth counseling with HIV-experienced obstetrician to address risks and benefits of conception |

How can HIV prevention be made a part of routine clinic practice?

HIV prevention, often neglected as a component of HIV clinical care, is more likely to be a part of routine clinic practice if it is part of the clinical continuous quality improvement activities (see Chapter 17: Quality Improvement). While the most effective indicators for prevention practice in the clinical setting are not known, considerations include medical record documentation of risk assessment history, prevention counseling, medical/laboratory examination for STDs, establishment of a prevention plan, and completion of referrals. There should be regular assessment of whether such tasks are completed and regular feedback to staff members regarding the success rates of completing these interventions. Finally, training interventions should be guided by data from these quality improvement activities (see Chapter 18).

KEY POINTS

The HIV clinical care setting offers an ongoing opportunity to work with patients to reduce their risk of transmitting HIV to others.

Common elements of behavioral interventions to reduce HIV risktaking include establishing rapport with the patient, addressing immediate patient needs (eg, mental health problems, substance abuse, housing), and working in small steps to build motivation and skills for change.

A brief history of patient risk behaviors and HIV prevention counseling should be parts of each patient visit.

Besides HIV prevention counseling, the following are important components of HIV prevention in the clinical setting: contact notification, drug abuse treatment, screening for STDs, decreasing the patient's viral load through ART, and nPEP.

Structural interventions for HIV prevention include making available educational materials and condoms, establishing strong referral relationships with social service and substance abuse services, and incorporating prevention indicators into quality improvement activities.



SUGGESTED RESOURCES

Institute of Medicine/Committee on HIV Prevention Strategies in the United States. *No time to lose: getting more from HIV prevention*. Ruiz MS, Gable AR, Kaplan EH, Stoto MA, Fineberg HV, Trussell J, eds. Washington DC: National Academy Press. 2001.

Centers for Disease Control and Prevention. *Advancing HIV prevention: New strategies for a changing epidemic – U.S. 2003*. *MMWR*. 2003;52:329-332. Available at <http://www.cdc.gov/hiv/pubs/mmwr.htm>.

Centers for Disease Control and Prevention. *Incorporating HIV prevention into the medical care of persons living with HIV*. *MMWR*. 52(RR12):1-24. July 18, 2003. Available at: <http://www.cdc.gov/hiv/pubs/guidelines.htm#prevention>.



WEBSITES

AIDSInfo: <http://www.AIDSInfo.nih.gov>
Accessed 11/03.

HIVInsite: <http://www.hivinsite.org?InSite?page=Prevention> Accessed 11/03.

STD/HIV Prevention Training Centers (PTCs): <http://depts.washington.edu/nnptc>
Accessed 10/03.

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Chapter 5:

Antiretroviral Therapy

John G. Bartlett, MD

THE PRINCIPLES OF ANTIRETROVIRAL THERAPY (ART)
WHEN TO START THERAPY
WHAT TO START
WHEN TO CHANGE THERAPY
WHAT TO CHANGE TO
RESISTANCE TESTING
KEY POINTS
SUGGESTED RESOURCES
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5

THE PRINCIPLES OF ANTIRETROVIRAL THERAPY (ART)

What are the goals of therapy?

The overall objective of treatment for HIV disease, as with treatment for many other infectious diseases, is to control the putative agent with antimicrobial agents while providing other appropriate therapies for HIV-related complications. The single most important goal of HIV antiretroviral therapy is to reduce the HIV viral load to as low as possible for as long as possible. The 5 other goals of antiretroviral therapy (ART) are to

- Prevent HIV-associated complications
- Avoid the long-term and short-term adverse drug reactions associated with antiretroviral agents
- Prevent HIV transmission
- Avoid HIV resistance
- Preserve HIV treatment options

Does antiretroviral therapy work?

Treatment recommendations have evolved greatly since zidovudine (AZT), a nucleoside, was first tested in 1986. The strategy was revolutionized in 1996-97 with the introduction of protease inhibitors (PIs) and then subsequently non-nucleoside reverse transcriptase inhibitors (NNRTIs). Combined with AZT and other nucleosides (see Table 5-1), the result was potent combination ART (also referred to as highly active antiretroviral therapy, or HAART) that had an immediate and dramatic impact on the prognosis for HIV infection, in fact one of the most impressive changes in any disease since the introduction of penicillin in the 1940s. Within 2 years there was a 60%-80% decrease

in mortality, AIDS rates, and hospitalizations for HIV-associated complications. Nevertheless, this treatment was also associated with some disappointments: there is still no cure for HIV infection, many of the patients given ART develop serious side effects, and drug resistance causes many patients to eventually have virologic failure so that long-term benefit may be difficult to sustain. Also, adherence has been shown to be critical to treatment success, and the level of adherence required is among the stiffest for the treatment of any disease in medicine.

See Glossary of Antiretroviral Drugs on page viii and the Pocket Guide

WHEN TO START THERAPY

What are the criteria for starting therapy?

The decision to start therapy, like most medical decisions, depends on the risk-to-benefit ratio of treatment. ART is given to control HIV replication and the consequent immune dysfunction, but therapy is also associated with the development of some substantial side effects and the risk of developing resistance that would limit future options. The reduction in CD4 cells is the pivotal event of HIV disease that renders the patient susceptible to the unique opportunistic infections (OIs) and tumors that have come to be known as AIDS-defining diagnoses (see Table 5-2). The patient becomes vulnerable to these diseases when the CD4 cell count decreases from normal levels (500-1500 cells/mm³) to <200 cells/mm³; the association with complications is the rationale for this CD4 cell threshold to be used by CDC to define AIDS.

Virtually all guidelines in the world have reached a consensus that a CD4 cell count of <200/mm³ is an indication for ART. The only question is the CD4 level above which treatment should be started. According to the DHHS Guidelines for the Use of Antiretroviral

Agents in HIV-Infected Adults and Adolescents (available at <http://www.aidsinfo.nih.gov>) the CD4 cell count range of 200-350/mm³ is also an indication for ART, but the decision is tempered by the viral load, the rapidity of the CD4 cell count decline (CD4 cell slope), and patient readiness. The role of viral load in this decision is based on 2 observations: 1) the viral load is an independent predictor of progression and 2) the CD4 decline slope is directly correlated with viral load. The implication is that a high viral load imparts a risk for more rapid progression to AIDS and a more rapid decline in the CD4 cell count. The threshold that appears important in the CD4 cell strata of 200-350 is ≥20,000 copies of virus/mL (c/mL). Some authorities also treat patients with a viral load of 50,000-100,000 c/mL even when the CD4 cell count is > 350/mm³, but there is no consensus here. It should be emphasized that multiple cohort studies involving thousands of patients clearly indicate that therapy is necessary when the CD4 cell count is < 200/mm³; some of these studies also show a benefit when the CD4 cell count is 200-350/mm³, but these findings are somewhat inconsistent from study to study.

What patient factors influence this decision?

Patient readiness may be the most important factor in the decision to treat most patients. ART is never an emergency, although the CD4 cell count clearly indicates the magnitude of risk from waiting. Most experienced HIV providers will never start ART on the first patient visit, which is designed for evaluation and the initiation of patient education. The patient must understand not only the risks and benefits of HIV treatment, but also the critical role of adherence to what may be one of the most complicated medical treatment regimens for any disease (see Chapter 7: Adherence to HIV Therapies).

WHAT TO START

How do you suppress HIV replication?

The goal of treatment is to suppress HIV as much as possible for as long as possible. This requires 3-4 drugs in combinations that have been proven to have merit in clinical trials (see Table 5-1).

Do you ever start with 1 or 2 drugs?

No, with a rare exception; some providers treat pregnant women with a CD4 cell count of > 350/mm³ and a viral load of < 1,000 c/mL with zidovudine (AZT) alone. With this exception, all patients should be treated with 3-4 drugs combined in a fashion that has established merit.

Table 5-1. Combination Antiretroviral Therapy

| |
|---|
| <p>Standard initial regimens</p> <ul style="list-style-type: none"> • 2 nucleosides* and a protease inhibitor (PI)** or a ritonavir-boosted PI • 2 nucleosides* and a non-nucleoside reverse transcriptase inhibitor (NNRTI)*** |
| <p>Classes</p> <p>* Nucleosides: zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), emtricitabine (FTC), abacavir (ABC), tenofovir (TDF) (tenofovir is actually a nucleotide rather than a nucleoside)</p> <p>** Protease inhibitors (PI): indinavir (IDV), ritonavir (RTV), nelfinavir (NFV), saquinavir (SQV; 2 formulations – Invirase and Fortovase), amprenavir (APV), fosamprenavir (FPV), lopinavir (LPV; co-formulated with ritonavir as LPV/r), and atazanavir (ATV)</p> <p>*** Non-nucleoside reverse transcriptase inhibitor (NNRTI): efavirenz (EFV), nevirapine (NVP), and delavirdine (DLV)</p> <p>Fusion inhibitors (used only for salvage): enfuvirtide (T20)</p> |

Table 5-2. When to Start Therapy

| Patient status | Recommendation | Comment |
|--|------------------------|--|
| Symptomatic HIV/AIDS | Treat | AIDS-defining diagnosis |
| Asymptomatic with CD4 cell count of >350/mm ³ | Defer therapy | Some authorities treat if viral load is >55,000 c/mL |
| CD4 cell count of 200-350/mm ³ | Treat or defer therapy | Influencing factors include <ul style="list-style-type: none"> • Patient readiness • CD4 slope (rate of decline) • Viral load (<20,000 c/mL = low risk of progression) • Treatment-associated risks: heart disease, drug interactions |
| CD4 cell count of <200/mm ³ | Treat | Universally accepted CD4 threshold for initiating treatment in all guidelines |

How do you decide on a specific regimen?

The selection of a regimen is based on the experience with completed trials and idiosyncrasies of the specific patients. No single regimen is appropriate for all patients, but virtually all experienced AIDS treaters have a few favorites. Most start with a 3- or 4-drug regimen that includes 1) an NNRTI combined with 2 nucleosides, 2) a PI either alone or boosted with ritonavir (RTV) plus 2 nucleosides, or 3) a 3-nucleoside regimen that includes abacavir (ABC), lamivudine (3TC), and zidovudine (combined as Trizivir). This last regimen has been popular for patients who struggle with complicated medical regimens because it is only 1 pill twice a day; however, the regimen is considered suboptimal compared with the PI- or NNRTI-based regimens.

Is once-a-day therapy possible?

This is now feasible and clearly preferred by some patients. The following drugs may be given once a day: tenofovir (TDF), lamivudine (3TC), emtricitabine (FTC), didanosine (ddI), stavudine (d4T), efavirenz (EFV), atazanavir (ATV), and amprenavir plus ritonavir (APV/r).

WHEN TO CHANGE THERAPY

When do you change therapy because of virologic failure?

The goal of therapy is to reduce the viral load to undetectable levels. The expectation is a reduction by 1 log₁₀ c/mL within 1-4 weeks, a viral load of < 500 c/mL at 16-24 weeks, and a viral load of < 50 c/mL after 24 weeks. Viral load measurements are subsequently made at 3-month intervals and are expected to remain at < 50 c/mL. Temporary increases above this level are sometimes called “blips.” Virologic failure is defined as 2 consecutive viral load counts of > 500 c/mL (see Table 5-3).

What causes virologic failure?

There are 2 causes: 1) resistance, meaning that the strain of HIV is resistant to one or more of the drugs in the regimen, and 2) failure of the drug to reach the virus, which may be due to failure of adherence, drug interactions, or drug malabsorption. The most common cause is lack of adequate adherence.

Table 5-3. Rationale for Changing Therapy

| Problem | Definition | Intervention |
|--------------------------|--|--|
| Virologic failure | Failure to decrease viral load to <500 c/mL within 16-24 weeks or achieving that goal with subsequent elevation to >500 c/mL with at least 2 measurements Causes: non-adherence, resistance or pharmacologic issues (poor bioavailability, drug interaction, etc.) Consequences: viral replication with progression of immunodeficiency and accumulating resistance mutation | Change drugs, usually based on sensitivity tests |
| Drug toxicity | Side effects that may be 1) annoying (GI intolerance, asthenia), 2) life-threatening (pancreatitis, lactic acidosis, hypersensitivity, hepatic necrosis), 3) cosmetic (fat redistribution), or 4) pose ill-defined risks (hyperlipidemia) | Substitute a different drug |

What do you do when the patient has side effects or intolerance to the regimen?

Side effects of antiretroviral agents are common and highly variable in severity and implications. Nausea is particularly common and may become a huge impediment to adherence. Other side effects may be more serious in terms of specific medical consequences, including several that are potentially lethal: pancreatitis due to didanosine (ddI), hypersensitivity due to abacavir (ABC), Stevens-Johnson syndrome due to an NNRTI, nevirapine-associated hepatic necrosis, and lactic acidosis due to nucleosides, especially stavudine (d4T). If the side effect precludes adherence or is regarded as a serious consequence for adherence, the regimen must be changed. It is important to warn patients about common and serious side effects before treatment begins.

Are there other forms of treatment failure?

Immunologic failure, as opposed to virologic failure, is characterized by the failure of the CD4 count to rebound, and clinical failure is characterized by AIDS-defining events (see Table 5-4). Success in treatment is based on viral load response, and this dictates therapy decisions. No one knows what to do with immunologic or clinical failure if there is viral suppression.

| Table 5-4. Definitions of Therapeutic Failure | |
|--|--|
| Type | Definition |
| Virologic failure | Initial therapy: failure to decrease viral load by 1 log ₁₀ c/mL by 1-4 weeks, to <500 c/mL by 8-16 weeks, or to <50 c/mL by 16-24 weeks. Chronic therapy: viral load >400 c/mL with 2 measurements after achieving viral suppression. |
| Immunologic failure | Failure to increase CD4 to >25-50/mm ³ /year (this is an arbitrary definition; the average increase with viral suppression by the above definition is an increase of 100-150 c/mm ³ /year). |
| Clinical failure | HIV-related complication, usually an AIDS-defining condition after antiretroviral therapy for ≥3 months. |

WHAT TO CHANGE TO

How do you address intolerance or serious side effects?

Assuming virologic control has been achieved, the goal is to find a substitute for the offending agent. In most cases, this is simply a single drug substitution using an agent in the same class with comparable potency. For example, for zidovudine (AZT) intolerance, stavudine (d4T) is commonly substituted. For indinavir-associated nephrolithiasis, the usual tactic is to reduce the dose, increase fluid intake, or substitute another PI for indinavir (IDV).

What is intensification?

Intensification is the addition of a drug, usually a single drug, to enhance antiretroviral activity in a patient who has a good but suboptimal response to therapy. This needs to be done at a time when the viral load has not increased to too high a level; for example, most authorities consider a viral load of > 5,000 c/mL to be an indication for a completely new regimen. Common ploys for intensification are the addition of tenofovir (TDF) or abacavir (ABC), or a boosting of a PI with ritonavir (RTV) if that was not done initially.

How do you deal with virologic failure?

The usual method is to measure HIV resistance. If the strain is sensitive, it is important to closely examine the adherence issue or look for drug interactions or some other reason that the antiretroviral agent does not reach the virus. If the virus is resistant, this information is used to select the next regimen as described below.

RESISTANCE TESTING

What are the tests?

There are 2 types of resistance tests: genotypic and phenotypic. Genotypic resistance measures mutations to the genes that are the target of antiretroviral drugs. These mutational changes predict resistance. Phenotypic resistance measures the activity of various drugs against the patient's virus compared with "wild type" virus (untreated HIV strains). These tests are quite different in method of performance, but there is no consensus regarding their relative merit. Many people use genotypic resistance testing most frequently because it is faster and cheaper. Under any circumstances, interpreting both tests requires substantial expertise. It should be emphasized that the testing is valid only for the drugs that are being given at the time the test is done; drugs discontinued > 2-6 weeks earlier may not be reliably tested because the resistant strains often become "minority species" when drug pressure is removed. Thus, a history of prolonged ART and virologic failure in the past often indicates resistance even if this is not revealed with the current test.

What are the indications and requirements for resistance testing?

The major indication for resistance testing is virologic failure, but testing is also sometimes done prior to initiation of therapy (see Table 5-5). The requirement for testing after virologic failure is an adequate viral load (usually > 1,000 c/mL) to do the test. For patients who have failed therapy it is standard practice to sample while the drugs of interest are being given. Resistance to drugs discontinued > 2-6 weeks before testing may not be expressed in the resistance testing, although this probably differs by individual patient and specific agent and has not been extensively studied.

| Patient status | Recommendation | Comment |
|--|---|--|
| Primary HIV infection | Consider testing | There are no studies to show use in this setting alters outcome of therapy, but the viral population is presumed to be relatively homogeneous, giving theoretical reliability to testing. |
| Chronic infection – treatment-naive | Consider testing | The concern is that resistant HIV may be archived making the test less reliable. Testing at this stage is best for predicting which agent will not work. |
| Chronic infection – treatment failure on therapy | | |
| <ul style="list-style-type: none"> • <i>First failure</i> | Recommended if testing requirements are met | Need viral load of >1000 c/mL to do the test. Patient may need to be receiving the antivirals that failed at the time of the test for resistance to be expressed. |
| <ul style="list-style-type: none"> • <i>Multiple failures</i> | Recommended if testing requirements are met | Resistant strains from prior therapy may not be expressed in the majority of strains tested; it is important to select next a regimen based on the current resistance test results, prior resistance tests, and treatment history. |

How should you treat someone who has run out of options?

Extensive use of ART over several years combined with virologic failure and resistance leads to limited options for many patients. However, it appears that antiretroviral drugs are still beneficial in these patients because of reduced “fitness” of the virus. The implication is that the antiretroviral drugs force development and persistence of resistant mutations, and these mutated strains have reduced replicative capacity in vitro and presumably in vivo as well. Several studies show that discontinuation of ART is often followed after 4-8 weeks by a significant

increase in viral load and a very rapid decline in the CD4 cell count. Thus, the goal of therapy for heavily treated patients who have few therapeutic options is often to continue these drugs despite virologic failure with the hope of maintaining the CD4 cell count and preventing HIV-related complications. Virologic control would be nice, but may be impossible or unrealistic.

What is therapeutic drug monitoring (TDM)?

TDM is the measurement of serum concentrations of antiretroviral drugs to determine if there are adequate levels to assure antiviral activity or to account for toxicity. Relatively few laboratories offer the test, and interpretation is confounded by limited experience and great variability among laboratories testing the same samples. Nucleosides are not tested because this would require measuring intracellular concentrations. It is usually PIs, which may have marginal levels, and to a lesser extent NNRTIs that are tested. Although TDM is not common in clinical practice at present, many experts feel it may become a standard component of treatment in the future with better standardization and more information about how to use the tests. The anticipated use is in situations in which levels are difficult to predict, as in renal failure, hepatic failure, pregnancy, concurrent use of drugs with possible drug interactions, use of once-a-day PIs with concerns about trough levels, and the monitoring of adherence.

When is structured treatment interruption (STI) indicated?

Although there are 4 reasons to suspend treatment temporarily, pulse therapy appears to be the most promising.

- **Immunization** One rationale for STI, when used with patients who have prolonged virologic control, is to stop therapy to let the virus come back and “immunize” the patient in a fashion analogous to a vaccine. The theory seemed good, but has not proven successful, and most have abandoned this tactic except with the rare patient who was treated very early in the course of the disease.
- **Treatment failure** A rationale for discontinuing treatment when it has failed due to drug resistance is to allow growth of “wild type virus” that is sensitive to antiretroviral agents. The theory, that STI would permit a new round of therapy against sensitive virus, has not proven successful for possibly predictable reasons. In many or most patients, the resistant strains are minority species that quickly become the dominant strains under renewed antiviral pressure.

- **Intermittent therapy** The plan with intermittent therapy is to periodically discontinue treatment on a prearranged schedule, such as 1 week on and 1 week off or 5 days of treatment followed by a weekend off. The theory is that when therapy is discontinued there is usually sustained viral suppression for 10-14 days and treatment is restarted while the virus is still suppressed. This strategy could potentially reduce treatment-associated side effects and cost. Although the initial experience has been limited but promising, the strategy cannot be recommended until more substantial experience is gained.
- **Pulse therapy** With this strategy, therapy is discontinued when the CD4 cell count increases to a level that makes the patient and physician comfortable doing so and is restarted when the CD4 count declines to a worrisome level. Initial experience has generally been that the viral load returns within 2 weeks and the CD4 cell count declines rapidly and then plateaus. Most experts restart therapy when the CD4 cell count reaches $350/\text{mm}^3$, but this strategy has not been systematically studied. Nevertheless, it does appear that there is no penalty in terms of resistance and the period off therapy is often 1-2 years, depending to a large extent on the CD4 cell count at the time treatment is discontinued and on the pre-therapy CD4 nadir. The patient must be warned that viral loads will return to pre-therapy levels, with important implications for risk of HIV transmission to others.

KEY POINTS

The major indicator for the speed of progression in early stage disease is the viral load, which dictates the speed of CD4 cell decline. The major indicator for the risk of HIV-associated complications is the CD4 cell count.

ART is directed toward preventing HIV-associated complications and hospitalizations and improving quality of life and survival.

ART does not cure HIV infection, is expensive, is associated with substantial risks of short-term and long-term toxicity, and requires a level of adherence that is unmatched with any other antimicrobial therapy.

ART is recommended when there are HIV-associated symptoms or when the CD4 count is $< 200\text{-}350/\text{mm}^3$.

The standard of practice for ART is 3 or 4 drugs representing 2 classes.

The major objective of ART is to inhibit HIV as reflected by viral load. Successful antiviral therapy is defined as a viral load of $< 50\text{ c/mL}$ by 16-24 weeks, usually accompanied by an increase in the CD4 cell count of $100\text{-}150/\text{mm}^3/\text{year}$.

Failed therapy is defined as virologic (viral load $> 400\text{ c/mL}$ twice after 24 weeks), immunologic (CD4 count fails to increase by $> 25\text{-}50/\text{mm}^3$ at 6-12 months), or clinical (new AIDS-defining OI after > 3 months of therapy).

Treatment is changed for drug intolerance (substitution) or virologic failure (selection by resistance tests).

The 3 factors that consistently predict outcome are CD4 cell count, patient adherence, and provider experience.



SUGGESTED RESOURCES

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Youle M. Strategies of HIV Management – When to start. *AIDS*. 2002;16:S145-149.



WEBSITES

AIDSInfo: <http://www.aidsinfo.nih.gov>
Accessed 11/03 (Several treatment guidelines are continuously updated at this U.S. Department of Health and Human Services website)

**AIDS information -
<http://www.aidsinfo.nih.gov>
for continuously updated
treatment guidelines**

CASES

1.

A 36-year-old woman is asymptomatic and has a CD4 cell count of $210/\text{mm}^3$ and a baseline viral load of $>750,000$ copies/mL. Other laboratory studies are unremarkable. She seeks your advice regarding management.

Question: What can you recommend?

- zidovudine (AZT) plus stavudine (d4T) plus efavirenz (EFV)
- lamivudine (3TC) plus zidovudine plus nelfinavir (NFV)
- Trizivir (AZT + 3TC + ABC) plus lopinavir/ritonavir (LPV/r)
- Trizivir
- lamivudine plus stavudine plus indinavir (IDV)

Answer:

Virtually all of these are feasible except option a, which combines zidovudine and stavudine, a combination that shows pharmacologic antagonism. The worrisome part of her presentation is that the CD4 cell count is quite low and approaching the threshold of vulnerability to opportunistic infections, and the viral load is very high, which poses substantial challenge to virologic control. The best drugs for baseline high viral load according to currently available data are 2 nucleosides combined with efavirenz or lopinavir/ritonavir. Thus, option c would be the best choice.

2.

A 42-year-old truck driver has HIV infection that was treated in 1999 with efavirenz (EFV), stavudine (d4T), and lamivudine (3TC). He subsequently did well and maintained a viral load of <50 c/mL, and the CD4 cell count increased from 250 to $450/\text{mm}^3$. He feels well, is fully adherent with his regimen by history, and has no complaints except that he is bothered by facial thinning (buccal cheek atrophy).

Question: Which of the following would you recommend?

- Discontinue treatment
- Change stavudine to abacavir (ABC)
- Switch efavirenz to indinavir (IDV) plus ritonavir (RTV)
- Switch stavudine to zidovudine
- Give zidovudine, lamivudine, and abacavir

Answer:

Discontinuing therapy is an option, although guidelines on when and how to do this are sparse because it has not been extensively studied. Anecdotal information suggests that this patient will have a sustained period with a CD4 cell count above the threshold for initiating treatment by current guidelines of $200\text{--}350/\text{mm}^3$. The best predictor of a prolonged drug-free interval is the baseline CD4 cell count, which in his case is low, but not severely low. The main problem is that the CD4 cell count at $450/\text{mm}^3$ is high, but possibly not high enough. The most likely cause of his change in face appearance is stavudine, but methods to reverse the change are not necessarily clear. If we stop stavudine, face thinning will not progress and some studies suggest there may be reversal after a prolonged period. Since this is important to the patient and this kind of change is relatively easy to make, we should probably do it, so the best answers are to use a potent regimen without stavudine treatment (options a, b, and d).

3.

A 36-year-old woman sees you for evaluation of HIV infection, which she has had since 1985. There have been multiple courses of treatment, including nucleosides in the period 1987 to 1996 and since then nucleosides combined with NNRTIs and PIs. The longest course of treatment was with zidovudine (AZT), lamivudine (3TC), and efavirenz (EFV), which produced a temporary period of virologic control but then failed. Currently she is receiving amprenavir (APV), lopinavir/ritonavir (LPV/r), and tenofovir (TDF). You perform a resistance test, which shows mutations on the reverse transcriptase gene at codons 41, 210, and 215 and mutations on the protease gene at 30 and 82. The conclusion is that HIV is resistant to most NRTIs and PIs. Her current numbers show a CD4 cell count of 87/mm³ and a viral load of 210,000 c/mL.

Question: What would you recommend?

- a. zidovudine plus lamivudine plus tenofovir plus efavirenz
- b. lopinavir/ritonavir plus efavirenz plus tenofovir
- c. AZT/3TC/ABC (Trizivir) plus lopinavir/ritonavir
- d. AZT/3TC/ABC plus tenofovir plus indinavir (IDV) plus ritonavir (RTV)
- e. enfurvirtide (T-20) plus atazanavir plus lamivudine plus tenofovir

Answer:

The tricky part of this question is the need to assume resistance to efavirenz and lamivudine despite the failure to demonstrate the associated mutations: 103 and 184 on the RT gene. This reflects the fact that these drugs were not being given at the time the test was done, but history suggests that resistance to these drugs occurred at the time of failure. The point is that interpretation of resistance tests must take into account both the current pattern and the history of drug exposure in terms of specific agent, duration, and virologic outcome. This patient is running low on options and low on CD4 cells. She does have some PI options, but the most predictable response would probably be a regimen with the fusion inhibitor enfurvirtide (option e).

4.

A 50-year-old secretary has just learned that he has HIV infection with a CD4 cell count of 49/mm³ and viral load of 280,000 c/mm³. He is quite shaken by this information, claims that he has never been able to take pills for anything and wants treatment, but wants it to be as simple as possible.

Question: What would you recommend?

- a. Delay therapy until the patient is ready
- b. AZT/3TC/ABC (Trizivir) plus efavirenz (EFV)
- c. tenofovir (TDF), lamivudine (3TC), plus efavirenz
- d. zidovudine (AZT), lamivudine, amprenavir (APV), and ritonavir (RTV)
- e. AZT/3TC/ABC (Trizivir)
- f. zidovudine plus efavirenz plus indinavir (IDV)

Answer:

This patient needs to be treated rapidly because he is highly vulnerable to major opportunistic infections. We emphasize the need for patient readiness, but this patient does not have much time to get ready. Training will take substantial effort as described in Chapter 7: Adherence to HIV Therapies. We would like potency plus convenience to facilitate adherence. The combination of lamivudine plus tenofovir plus efavirenz (option c) means 4 pills once a day, which could be taken, for example, when he shaves.

5

5.

A doctor telephones you about a patient who has read about structured treatment interruption for patients who have failed therapy. You are told this patient has extensive experience with antiretroviral treatment for over 10 years, a CD4 cell count of 80-100/mm³, and a viral load that is back to baseline at 420,000 c/mL.

Question: What would you recommend to the physician?

- a. Test resistance while receiving antiretroviral drugs and select the drugs based on the ART history and resistance tests
- b. Discontinue treatment, test the HIV strain at 12 weeks, and treat accordingly
- c. Continue therapy with same drugs
- d. Treat with lopinavir/ritonavir (LPV/r), Trizivir (AZT/3TC/ABC), tenofovir (TDF), and either efavirenz (EFV) or nevirapine (NVP)

Answer:

The experience with STI for virologic failure is that wild-type virus that is less resistant replaces the predominant strain after about 6-11 weeks, but the CD4 cell count drops rapidly during the period off treatment; after new treatment, the more completely resistant pre-STI strain returns. The largest experience indicates only about 10%-15% of these attempts have been judged successful. Therefore, STI for virologic failure has fallen into disfavor. Nevertheless, if you wanted to play long odds, the right time to do the testing is after there has been a sufficient interval for ingrowth of a new, more sensitive strain of HIV making option b the correct option. However, most would prefer option a with expert interpretation of the test results.

6.

Question: Which of the following patients is the best candidate for genotype resistance testing?

- a. A previously untreated pregnant woman with HIV
- b. A chronically infected, previously untreated man with a partner who is currently taking triple therapy with poor control
- c. A woman who has failed her initial treatment with a viral load of 7,000 c/mL after 1 year on indinavir (IDV), ritonavir (RTV), lamivudine (3TC), and stavudine (d4T)
- d. A 40-year-old man with good virologic control, but a need to change therapy because of AZT-induced anemia

Answer:

Recommendations for the use of resistance testing are somewhat arbitrary, but the highest priority according to virtually all guidelines is for patients who have failed treatment for the purpose of identifying the next regimen; therefore, option c is the best answer.

Chapter 6:

Metabolic Complications of Antiretroviral Therapy

David H. Spach, MD

OVERVIEW
LIPID ABNORMALITIES
LIPODYSTROPHY
LACTIC ACIDOSIS
OTHER METABOLIC COMPLICATIONS

KEY POINTS
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OVERVIEW

What is meant by metabolic complications of antiretroviral therapy (ART)?

Metabolic complications refers to a group of adverse drug reactions that have been associated with long-term use of antiretroviral drugs, which include:

- Lipid abnormalities
- Lipodystrophy
- Lactic acidosis
- Hyperglycemia
- Decreased bone mineral density

See Glossary of Antiretroviral Drugs on page viii and the Pocket Guide

Each adverse reaction is more commonly associated with a specific class of antiretroviral drugs, and the agents within the class that cause the reactions do so with variable frequencies. In most cases, the pathophysiologic mechanism of the changes is unknown. The classes of drugs associated with each major adverse reaction are listed in Table 6-1.

What metabolic toxicities should you monitor for in patients taking ART?

Recommendations for monitoring patients for ART-related metabolic complications, listed in Table 6-2, are discussed in detail in the sections below.

Table 6-1. Adverse Reactions of Classes of Antiretroviral Drugs

| Adverse Reaction | Cause | | |
|--------------------------|--------|----------|-------|
| | NRTIs* | NNRTIs** | PI*** |
| Lactic acidosis | ++ | - | - |
| Lipid changes | | | |
| Elevated triglycerides | - | (+) | ++ |
| Elevated LDL cholesterol | - | + | ++ |
| Insulin resistance | - | - | ++ |
| Fat redistribution | | | |
| Fat atrophy | + | - | - |
| Fat accumulation | - | - | ++ |

* NRTIs = Nucleoside and nucleotide reverse transcriptase inhibitors
 ** NNRTIs = Non-nucleoside reverse transcriptase inhibitors
 *** PIs = Protease inhibitors
 (+) = possibly causes adverse reaction
 + = sometimes causes adverse reaction
 ++ = frequently causes adverse reaction

LIPID ABNORMALITIES

What antiretroviral medications adversely affect lipid levels?

Available data suggest that drugs in the protease inhibitor (PI) class have the greatest adverse effect on triglycerides, total cholesterol, and low-density lipoprotein (LDL) cholesterol levels. The mechanism remains unclear. Among the PIs, ritonavir (RTV) and ritonavir-boosted regimens appear to have the greatest impact on triglycerides and total cholesterol levels. Because some patients who receive ritonavir had no significant changes whereas others have dramatic increases, genetic predisposition may play a major role. The PI atazanavir (ATV) does not significantly affect lipid levels. The impact of nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) on lipid levels has not been well defined, but the impact appears much less than changes associated with PIs. In 96-week data from a trial that compared stavudine (d4T) plus lamivudine (3TC) plus efavirenz (EFV) with tenofovir (TDF) plus

lamivudine plus efavirenz, those patients in the stavudine arm had significantly higher cholesterol and triglyceride levels. The NNRTI nevirapine (NVP) has no adverse affect on lipids, and the changes with efavirenz are variable. Patients receiving PIs should undergo regular monitoring of lipid levels (see Table 6-2).

Do antiretroviral drugs cause an increase in cardiovascular disease?

Several isolated case reports initially suggested ART could lead to cardiovascular disease, including death from myocardial infarction, in HIV-infected patients. More recent aggregate data from over 20,000 patients in cohort studies indicate the risk related to ART is low and substantially lower than the risk of smoking (Friss-Moller, et al, 2003). In addition, in a large study that involved more than 36,000 veterans, investigators found the benefit of these drugs far outweighed the risks. Because cardiovascular disease may take 10-15 years to manifest, investigators will need long-term followup of individuals who have received ART to determine the long-term impact.

6

Table 6-2. Recommendations for Assessment and Monitoring of Metabolic Complications of Antiretroviral Therapy for HIV Infection

| | |
|--|--|
| Glucose and lipid abnormalities | <ul style="list-style-type: none"> The following assessments are recommended before initiation of potent ART, at the time of a switch of therapy, 3 to 6 months after starting or switching therapy, and at least annually during stable therapy: <ul style="list-style-type: none"> Fasting glucose (if therapy includes a PI) Fasting lipid panel (total cholesterol, HDL, and LDL cholesterol [calculated or direct], and triglyceride levels) A blood glucose level after oral administration of 75 g of glucose may be used to identify impaired glucose tolerance in patients with risk factors for type 2 diabetes mellitus or those with severe body fat changes. |
| Body fat distribution abnormalities | <ul style="list-style-type: none"> No specific technique can be recommended at the present time for routine assessment and monitoring of body fat distribution changes. |
| Lactic acidemia | <ul style="list-style-type: none"> Routine measurement of lactic acid levels is not recommended. Lactic acid levels should be monitored in those receiving NRTIs who have clinical signs or symptoms of lactic acidemia, and in pregnant women receiving NRTIs. If alternative NRTIs are resumed in those who have interrupted antiretroviral therapy for lactic acidemia, lactate levels should be monitored every 4 weeks for at least 3 months. |
| Osteopenia, osteoporosis, and osteonecrosis | <ul style="list-style-type: none"> Routine screening for osteoporosis or osteonecrosis is not recommended. Radiographic examination of involved bone is recommended for those with symptoms of bone or joint pain; the contralateral joint should also be assessed. |
| DEXA = dual-energy x-ray absorptiometry HDL = high-density lipoprotein LDL = low-density lipoprotein NCEP = National Cholesterol Education Program NNRTI = non-nucleoside reverse transcriptase inhibitor NRTI = nucleoside reverse transcriptase inhibitor | |
| Source: Schambelan M, Benson CA, Andrew Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: Recommendations of an International AIDS Society-USA Panel. <i>J Acquir Immune defec Syndr</i> . 2002;31:269. Reprinted with permission of Lippincott Williams and Wilkins. http://www.com . | |

Should you treat abnormal lipid levels in HIV-infected persons?

Although prospective studies have not clearly defined the long-term adverse cardiovascular effects associated with hyperlipidemia in HIV-infected persons, abnormal lipid levels appear to pose the same long-term risks as have been well established in persons who do not have HIV infection and thus need to be managed appropriately (see Table 6-3). Accordingly, clinicians should address abnormal lipid levels and the individual patient risks, including prior cardiovascular events, smoking, hypertension, diabetes, family history, obesity, and baseline lipid levels. The potential interventions include 1) switching to a regimen less likely to cause abnormal lipids (if possible without sacrificing antiviral effectiveness), 2) implementing dietary changes, 3) using a lipid-lowering agent according to

recommendations in Table 6-4, and 4) addressing other lifestyle habits that affect cardiovascular risk, such as smoking and exercise.

What statins are recommended for treating patients on PIs?

Significant drug interactions may occur with PIs and lipid-lowering statins; for patients on PI-based ART, most experts consider pravastatin and atorvastatin as preferred statins and avoid using lovastatin or simvastatin. Initial therapy should consist of a low dose of either pravastatin (20 mg po qd) or atorvastatin (10 mg po qd), with monitoring of response to therapy and, if required, gradual and cautious increases in doses of the statin. Triglyceride levels in excess of 1000 mg/dL place the patient at risk for developing pancreatitis. Most experts recommend intervening

Table 6-3. Recommendations for Treatment of Metabolic Complications of Antiretroviral Therapy for HIV Infection

| | |
|--|--|
| Glucose intolerance and diabetes mellitus | <ul style="list-style-type: none"> • Weight loss for overweight subjects is recommended. • Follow established guidelines for treating diabetes in the general population, with preference given to insulin sensitizing agents such as metformin (except for those with renal disease or history of lactic acidemia) or thiazolidinediones (except for those with preexisting liver disease). • Avoid use of a PI as initial therapy in patients with preexisting glucose intolerance or diabetes mellitus. |
| Lipid and lipoprotein abnormalities | <ul style="list-style-type: none"> • Follow NCEP III guidelines for assessment of risk factors for cardiovascular disease, and dietary and lifestyle alterations for lowering cholesterol and triglyceride levels. • Avoid use of PIs, if possible, in those with preexisting cardiovascular risk factors, family history of hyperlipidemia, or elevated lipid levels. • Follow NCEP guideline thresholds for lipid-lowering therapy. • Fibrates are recommended as initial therapy for those with isolated fasting hypertriglyceridemia. • Pravastatin or atorvastatin are preferred statin agents for those with isolated fasting hypercholesterolemia requiring treatment in the setting of PI or other CYP 3A4 inhibitor therapy. • If combination therapy for hypercholesterolemia and hypertriglyceridemia is indicated, therapy should begin with a statin, followed by the addition of a fibrate if there is insufficient response after 3 to 4 months of treatment. |
| Body fat distribution abnormalities | <ul style="list-style-type: none"> • No therapies for fat distribution abnormalities in the absence of other metabolic complications can be routinely recommended. |
| Lactic acidemia | <ul style="list-style-type: none"> • ART should be withheld for all patients with confirmed lactate levels >10 mmol/L (90 mg/dL) or those with confirmed lactate levels >5 mmol/L (45 mg/dL) who are symptomatic. • No intervention apart from NRTI cessation is recommended. • Restart combination NNRTI and PI therapy after lactate levels return to normal and symptoms resolve. |
| Osteopenia, osteoporosis, and osteonecrosis | <ul style="list-style-type: none"> • Surgical resection of involved bone is the only effective therapy for symptomatic osteonecrosis. • If osteoporosis is demonstrated by radiography or regional DEXA scanning, or if a pathological fracture occurs in the setting of osteoporosis, therapy with a bisphosphonate should be considered. |

DEXA = dual-energy x-ray absorptiometry
 HDL = high-density lipoprotein
 LDL = low-density lipoprotein
 NCEP = National Cholesterol Education Program
 NNRTI = non-nucleoside reverse transcriptase inhibitor
 NRTI = nucleoside reverse transcriptase inhibitor

Source: Schambelan M, Benson CA, Andrew Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: Recommendations of an International AIDS Society-USA Panel. *J Acquir Immune defec Syndr*. 2002;31:269. Reprinted with permission of Lippincott Williams and Wilkins, <http://www.com>.

Table 6-4. Summary of National Cholesterol Education Program Treatment Recommendations Based on LDL Cholesterol*

| Risk Category | Initiate therapeutic lifestyle changes† | Consider drug therapy | LDL** cholesterol goal | Non-HDL** cholesterol goal |
|--|---|---|--------------------------|----------------------------|
| With CHD or CHD** risk equivalent (10-year risk >20%, noncoronary atherosclerotic vascular disease, or type 2 diabetes mellitus) | ≥100 mg/dL (≥2.6 mmol/L) | ≥130 mg/dL (≥3.4 mmol/L) 100–129 mg/dL (2.6–3.3 mmol/L): therapy optional | <100 mg/dL (<2.6 mmol/L) | <130 mg/dL (<3.4 mmol/L) |
| 2 or more risk factors (10-year risk <20%)‡ | ≥130 mg/dL (≥3.4 mmol/L) | 10-year risk of 10%–20%: ≥130 mg/dL (≥3.4 mmol/L) 10-year risk of <10%: ≥160 mg/dL (≥4.1 mmol/L) | <130 mg/dL (<3.4 mmol/L) | <160 mg/dL (<4.1 mmol/L) |
| 0 or 1 risk factor‡ | ≥160 mg/dL (≥4.1 mmol/L) | ≥190 mg/dL (≥4.9 mmol/L) 160–189 mg/dL (4.1–4.9 mmol/L): therapy optional | <160 mg/dL (<4.1 mmol/L) | <190 mg/dL (<4.9 mmol/L) |

* For patients with high triglyceride levels in whom LDL cholesterol cannot be measured, non-HDL cholesterol level (total cholesterol – HDL cholesterol) may be used as an approximation if 30 mg/dL (0.8 mmol/L) is added to the LDL cholesterol threshold. For those with triglyceride levels >200 mg/dL (2.3 mmol/L), the non-HDL cholesterol level is considered a secondary target of therapy and the goals of therapy are as indicated under the heading of non-HDL cholesterol goal.

‡ Risk factors include cigarette smoking; hypertension (blood pressure ≥140/90 mm Hg or taking antihypertension drugs); HDL cholesterol level below 40 mg/dL (1.0 mmol/L); family history of premature CHD (in first-degree male relatives <55 years and first-degree female relatives <65 years); age (>45 years for men and >55 years for women). Risk factor equivalent: diabetes. If HDL cholesterol is over 60 mg/dL (1.6 mmol/L), subtract 1 risk factor from the total.

† Therapeutic lifestyle changes refer to reducing saturated fat and cholesterol intake; enhancing the reduction in LDL cholesterol level by the use of plant stanols/sterols and increased soluble fiber; weight reduction; and increased physical activity.

** CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

Source: Schambelan M, Benson CA, Carr A, et al. Management of Metabolic Complications Associated with Antiretroviral Therapy for HIV-1 Infection: Recommendations of an International AIDS Society–USA Panel. *J Acquir Immune Defic Syndr*. 31:262. Nov 1, 2002. Adapted from Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–2497. Reprinted with permission of Lippincott Williams and Wilkins. <http://www.com>.

when triglyceride levels exceed 500 mg/dL. Although dietary changes can improve triglyceride levels, most patients with PI-associated hypertriglyceridemia will require pharmacologic intervention. Patients with isolated hypertriglyceridemia should receive a fibric acid derivative, either gemfibrozil (600 mg po bid) or fenofibrate (200 mg po qd). For those who have high triglyceride and LDL cholesterol levels, a statin drug should be used first with the plan of adding a fibric acid derivative after 4 months if the response to the statin is suboptimal. Because both the statin drugs and the fibric acid derivatives can cause rhabdomyolysis, caution should be used if these medications are given concurrently. In patients with severe hypertriglyceridemia refractory to a fibric acid derivative, some experts would recommend a trial of adding fish oil supplements to the lipid-lowering regimen.

Does switching ART improve lipid abnormalities?

Although some antiretroviral medications clearly have a greater adverse impact than others on lipids, modifying the regimen in an attempt to improve the lipid profile is sometimes difficult, mainly because of the need to maintain antiretroviral efficacy. Examples of possible changes likely to improve lipid abnormalities include switching a PI to either nevirapine (NVP) or using the alternative PI atazanavir (ATV). Changing from a PI to efavirenz (EFV) has not produced consistent results. Preliminary data from one study has shown that patients who switched from stavudine (d4T) to tenofovir (TDF) had a significant improvement in cholesterol and triglyceride levels. Future work will better determine whether changes from one nucleoside to another will affect lipid levels.

LIPODYSTROPHY

What is lipodystrophy?

Although lipodystrophy was first reported in the mid-1990's, investigators have not agreed on a standardized, objective definition for this disorder. Most researchers and clinicians loosely define lipodystrophy as any significant change in body morphology that does not result from either weight gain or weight loss. The general term lipodystrophy now typically includes 3 subsets of morphologic changes: generalized fat accumulation, focal fat accumulation, and fat atrophy. Fat accumulation most often occurs in the abdominal, breast, or dorsocervical region. Fat atrophy most often occurs as buccal fat pad atrophy (facial wasting) or subcutaneous fat wasting in the buttocks or extremities. Because a standardized definition for lipodystrophy is lacking, the incidence varies depending on the exact criteria investigators use to define lipodystrophy in their specific study. Tests for abnormalities in body fat distribution have included computed tomography (CT) scanning, magnetic resonance imaging (MRI), bioelectrical impedance analysis (BIA), DEXA (dual energy x-ray absorptiometry) scans, and anthropometric measurements. The CT and MRI tests are generally considered the most accurate, but not practical for routine screening purposes, primarily because of their high cost. Anthropometric measurements can estimate visceral adipose tissue and subcutaneous adipose tissue and can easily be performed in the clinic without major costs. Despite the many options available for measuring abnormalities in fat distribution, no technique has shown adequate sensitivity and specificity to recommend performing routinely.

What causes lipodystrophy in HIV-infected persons?

Despite intense investigation, the exact pathogenesis of lipodystrophy remains unclear. Initial reports linked PI use with lipodystrophy, but subsequent reports have identified lipodystrophy in patients who had never received a PI. Several studies have shown that the most important risk factors for development of lipodystrophy are a history of severe immune suppression (nadir CD4 count < 100 cells/mm³), older age, prolonged use of antiretroviral drugs, and highly active antiretroviral therapy. Investigators have found that patients with lipodystrophy often have high insulin levels and evidence of insulin resistance, a finding that suggests insulin resistance is associated with lipodystrophy, but does not prove that insulin resistance causes lipodystrophy. Many clinicians have observed that fat accumulation is more often associated with PI-based therapy, whereas fat wasting has been most closely linked to NRTIs, particularly stavudine (d4T). In 96-week data

from a trial that compared stavudine plus lamivudine (3TC) plus efavirenz (EFV) with tenofovir (TDF) plus lamivudine plus efavirenz, those patients in the stavudine arm had substantially higher rates of lipodystrophy.

Can fat redistribution be reversed?

First, it is important to evaluate the severity of the lipodystrophy, the degree to which the patient is bothered by the body changes, and how strongly the patient wants to try to reverse the lipodystrophy. Although fat redistribution does not appear to directly alter health outcome, many patients experience notable unfavorable changes in their physical appearance that may affect their quality of life. Moreover, these changes in body appearance may broadcast their HIV diagnosis. That lipodystrophy changes thus may even lead some to stop their antiretroviral medications. If lipodystrophy develops, there are 3 treatment options: 1) Switch therapy, meaning a substitution for the implicated drug. This usually involves a substitute for stavudine (d4T) if lipoatrophy has developed or a change to a non-PI-based regimen if fat accumulation has occurred. Initial results with switches showed limited success, and when there was a response it took a long time. More promising results were seen in a recent study in which replacing stavudine (d4T) with abacavir (ABC) or zidovudine (AZT) resulted in significant improvement after 48 weeks in patients with stavudine-induced lipoatrophy (McComsey, et al, 2004). 2) Drug therapy is another option. Metformin, thiazolidinediones, testosterone, other anabolic steroids, and growth hormone have been used with partial success with fat accumulation, but all have drawbacks and do not address the underlying lipoatrophy. 3) The third option is plastic surgery, which may be particularly useful for buccal fat atrophy or dorsothoracic fat accumulations; however, results have been highly variable, and these procedures are usually regarded as cosmetic surgery and not covered by insurance companies.

LACTIC ACIDOSIS

What are ART-related hyperlactatemia and lactic acidosis?

ART-related abnormalities of serum lactate levels (hyperlactatemia) range from asymptomatic hyperlactatemia to symptomatic hyperlactatemia with mild acidosis, to fulminant lactic acidosis, liver failure, and death. In addition, some patients develop hepatic steatosis. The development of fulminant lactic acidosis, although very rare, has clearly emerged as one of the most dreaded adverse effects associated with ART.

What antiretroviral drugs cause hyperlactatemia?

Hyperlactatemia and lactic acidosis result from abnormal mitochondrial toxicity caused by NRTIs that inhibit the critical enzyme mitochondrial DNA polymerase gamma. There is no evidence that NNRTIs or PIs cause mitochondrial toxicity or abnormalities in serum lactate levels. In vitro data and retrospective clinical data show that stavudine (d4T) and didanosine (ddI) are the most likely medications in the NRTI class to cause this complication, especially if used together. Zidovudine poses some risk but significantly less than either stavudine or didanosine. Tenofovir (TDF), abacavir (ABC), emtricitabine (FTC), and lamivudine (3TC) appear to pose the least risk of causing lactic acidosis. Identified risk factors, in addition to the use of NRTIs, include pregnancy, female gender, obesity, or concurrent treatment with ribavirin, hydroxyurea, or metformin.

How do you collect and interpret a serum lactate test?

The normal serum lactate level is < 2 mmol/dL. Proper blood collection and appropriate transport are essential for obtaining an accurate result. The patient should not exercise for 24 hours prior to the test and should be well hydrated, and should rest for at least 5 minutes prior to the blood draw. The blood should be drawn without tourniquet and the patient should be instructed not to clench his or her fist. The sample should be submitted promptly for processing using a pre-chilled fluoride-oxalate tube transported on ice. The specimen should be processed within 4 hours after being drawn.

For interpretation, levels of 2-5 mmol/dL are often associated with no symptoms, levels of 5-10 mmol/dL are usually associated with symptoms that require discontinuation of NRTIs, and levels of > 10 mmol/dL are associated with a fatality of > 30% and require immediate intervention. Abnormal levels should usually be confirmed.

How do you diagnose lactic acidosis?

Routine monitoring of serum lactate levels in asymptomatic patients is not recommended (see Table 6-2), but obtaining a serum lactate level is critical if hyperlactatemia is suspected (see previous question for correct technique). Patients with mild increases in serum lactate levels generally do not have significant symptoms, and if symptoms are present, they are most likely nonspecific. With more severe increases in serum lactate levels, patients may have marked fatigue,

nausea, anorexia, vomiting, abdominal pain, dyspnea, and hyperventilation. Although a chemistry panel may show a decreased serum bicarbonate level or increased anion gap level, some reports have documented patients with severe lactic acidosis who do not have abnormal serum bicarbonate or increased anion gap measurements. CT scan of the liver may show enlargement and fatty infiltration.

How do you manage severe hyperlactatemia or lactic acidosis?

Patients with severe hyperlactatemia or lactic acidosis should immediately discontinue ART (see Table 6-3). Seriously ill patients may require IV bicarbonate, mechanical ventilation, or dialysis. Most respond to drug withdrawal. Case reports have suggested improvement in lactic acidosis with use of compounds such as riboflavin, thiamine, L-carnitine, or co-enzyme Q, with the benefit hypothetically resulting from improvement in mitochondrial function; however, the use of these agents to prevent hyperlactatemia and lactic acidosis has not been studied. Unfortunately, even after discontinuing ART, recovery from lactic acidosis typically takes about 8 weeks, since regeneration of severely damaged mitochondria is a prolonged process.

Once a lactic acidosis episode is resolved, can a patient resume ART?

For those patients who recover from an episode of lactic acidosis, the optimal management of their subsequent ART remains unclear. For those patients who clearly need ART, the safest option would be to use a regimen that does not contain an NRTI, such as lopinavir plus ritonavir plus efavirenz (LPV/r + EFV), saquinavir plus ritonavir (SQV + RTV), or indinavir plus ritonavir plus efavirenz (IDV + RTV + EFV). Available data suggest tenofovir (TDF), lamivudine (3TC), emtricitabine (FTC), and abacavir (ABC) are the NRTIs least likely to cause severe hyperlactatemia or lactic acidosis. In a report of 17 patients who developed symptomatic hyperlactatemia while receiving stavudine (d4T), the patients were rechallenged with abacavir or zidovudine; none of the 17 had a recurrence of symptomatic hyperlactatemia. Nevertheless, providers should obtain expert consultation and also observe the patient closely when restarting a new regimen that includes one or more NRTIs in any patient with a history of lactic acidosis.

OTHER METABOLIC COMPLICATIONS

Does ART cause hyperglycemia and diabetes?

Although several studies have shown that PIs can have a direct effect on glucose metabolism, predominantly by increasing insulin resistance, it remains unclear whether ART significantly increases the risk for developing diabetes mellitus. Available data would suggest that ART, particularly with PIs, likely causes a slightly increased risk of developing overt diabetes mellitus. Routine monitoring for hyperglycemia is recommended for any patient on a PI-based regimen (see Table 6-3). Studies of patients with hyperglycemia and insulin resistance have consistently shown that switching from a PI to either nevirapine (NVP), efavirenz (EFV), or abacavir (ABC) will significantly improve the hyperglycemia and insulin resistance. Nevertheless, further study is needed to better clarify the risk of a patient's developing diabetes mellitus while taking a PI and the long-term clinical benefit of switching from a PI to a regimen that causes less insulin resistance.

Does ART cause abnormalities in bone density?

Several retrospective reports have suggested that ART may cause decreases in bone mineral density and, rarely, avascular necrosis. Recently, the relationship between ART and decreases in bone mineral density has become very controversial and prospective studies are needed to resolve the issue. From a clinical perspective, avascular necrosis should be suspected when a patient complains of focal bone pain; either CT or MRI can confirm the diagnosis. Avascular necrosis most often involves the femoral or humeral head, can consist of necrosis at a single or multiple sites, does not respond to medical therapy, and typically requires surgical intervention (see Table 6-3). There are no data regarding modifying an ART regimen either to prevent avascular necrosis or to improve the condition once it has already developed.

KEY POINTS

Metabolic complications include the long-term consequences of antiretroviral agents: lactic acidosis (due to NRTIs [nucleosides]), dyslipidemia (usually due to PIs), insulin resistance (usually due to PIs), fat redistribution (usually due to NRTIs and PIs).

All PIs except atazanavir (ATV) are associated with variable increases in the LDL cholesterol and/or triglycerides.

Cardiovascular risks of dyslipidemia associated with PI therapy are assumed to be the same as for persons without HIV infection; they are usually managed with lifestyle changes (smoking cessation, diet modifications, and exercise) and, if necessary, lipid-lowering drugs; if statins are used, pravastatin or atorvastatin are preferred to avoid drug interactions with the PIs.

Patients receiving PIs should have blood lipids and glucose monitored at baseline, at 3-6 months and then at least annually, and more frequently depending on other risks and severity of abnormalities.

ART is associated with fat redistribution, both fat accumulation (abdomen, breasts, dorsocervical) and fat wasting (buccal fat with face thinning, buttocks, and extremities). These changes can result in major unfavorable changes in physical appearance and can have a significant impact on quality of life.

There are no effective treatments for reversing fat redistribution. Discontinuing or switching therapy has moderate effect at best and improvement requires a very long time; with face thinning the best results are with discontinuing stavudine (d4T) early.

Lactic acidosis is a result of mitochondrial toxicity caused by prolonged use of NRTIs, primarily stavudine (d4T), didanosine (ddI) and to a lesser degree zidovudine (AZT).

The usual symptoms of lactic acidosis are fatigue, abdominal pain, nausea, and weight loss; the usual laboratory finding is a serum lactate exceeding 5 mmol/dL. The main treatment is to discontinue the implicated drugs or switch to NRTIs that are less likely to cause this.

Type 2 diabetes is an occasional complication of PI therapy due to insulin resistance. Monitoring should include fasting blood glucose at baseline and at 5-8 months with subsequent measurements depending on risk and prior results.



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CASES

1.

A 36-year-old HIV-infected man has received stavudine (d4T) plus lamivudine (3TC) plus indinavir (IDV) for approximately 4 years. This regimen was his first regimen and before starting therapy his HIV RNA was 59,000 copies/mL and his CD4 count was 34 cells/mm³. His antiviral and immunologic response has been excellent, with HIV RNA levels persistently less than 50 copies/mL and a CD4 count that has increased to 526 cells/mm³. In the past 9 months, however, he has developed hyperlipidemia, hyperglycemia, and body fat changes, most notably enlargement of his abdominal region and facial thinning. He has been very hesitant to change his regimen but now comes into the clinic to discuss this matter again.

Question: If he changes his antiretroviral regimen, will he likely continue to have excellent control of HIV?

Answer:

Since this patient has experienced excellent long-term viral suppression and this was his first regimen, it is highly likely that a switch from a PI to a NNRTI (efavirenz [EFV] or nevirapine [NVP]) would maintain continued viral suppression. Similarly, a change from one NRTI to another would likely have no adverse effect on HIV suppression. In patients who have previously developed resistance and are currently on a salvage regimen, changing a medication because of side effects can pose a much greater risk of not maintaining excellent virologic control.

Question: What improvements would he likely expect if he makes a change?

Answer:

Among the problems this patient has developed as a complication of ART, insulin resistance and hyperlipidemia are the most likely to improve with a regimen change. In particular, several studies have shown switching from a PI to either nevirapine, efavirenz, or abacavir (ABC) typically leads to significant improvement in hyperglycemia and insulin resistance. Improvements in lipids are most likely to occur if the PI is switched to either nevirapine or abacavir. Switching from one PI to the new PI atazanavir (ATV) may provide significant improvement in lipid abnormalities. Unfortunately, changing from a PI to an NNRTI has not produced reliable improvements in lipodystrophy. Changing from stavudine to either abacavir or tenofovir (TDF) may provide some improvement in lipodystrophy for some patients. Although tenofovir causes less lipodystrophy than stavudine, studies that examine the effect of changing stavudine to tenofovir have not been performed.

2.

A 33-year-old woman on stavudine (d4T) plus didanosine (ddI) plus efavirenz (EFV) presents with severe fatigue. No obvious cause for the fatigue is discovered and 1 week later she returns with even worse fatigue. Serum chemistries now are notable for a bicarbonate of 17 mmol/L. A serum lactate level is drawn and a lactate level of 6.3 mmol/L is reported from the laboratory. The patient is not taking any other medications and is not taking any herbal preparations.

Question: Is the serum lactate level of 6.3 mmol/L concerning in this patient?

Answer:

Experts have stratified serum lactate levels based on the risk of developing complications from hyperlactatemia. Those with a serum lactate level of 2.1-5.0 mmol/L are considered to have mild hyperlactatemia, those with a serum lactate level of at least 5 mmol/L have serious hyperlactatemia, and those with a lactate level at least 5 mmol/L plus a bicarbonate level less than 20 mmol/L have lactic acidosis. Accordingly, the patient's serum lactate of 6.3 mmol/L (along with the serum bicarbonate of 17 mmol/L) is extremely concerning and suggests lactic acidosis, a potentially life-threatening problem.

Question: If lactic acidosis is suspected, how should the patient be managed?

Answer:

Because hyperlactatemia and lactic acidosis result from NRTI-induced mitochondrial toxicity, the first step in managing this problem is to immediately discontinue ART. Although several case reports have suggested improvement in lactic acidosis by using compounds such as riboflavin, thiamine, L-carnitine, or co-enzyme Q, supportive care remains the mainstay of therapy. After discontinuing ART, regeneration of severely damaged mitochondria typically requires prolonged periods, and recovery from lactic acidosis can take several months. Following recovery, the optimal management of subsequent antiretroviral therapy remains unclear. Preliminary reports suggest changing the NRTIs (typically replacing stavudine) can safely be performed, but should be done with expert consultation.

Chapter 7:

Adherence to HIV Therapies

Laura W. Cheever, MD, ScM

OVERVIEW
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OVERVIEW

What is meant by medication adherence?

Medication adherence means a patient takes the prescribed dose of prescribed medications on the prescribed schedule, following prescribed dietary instructions. Patient adherence to medical appointments and to behaviors that minimize the risk of transmission of HIV to others correlates strongly with adherence to medications and is an important part of primary care of HIV-infected patients but will not be addressed in this chapter.

Why is medication adherence so important in HIV therapy?

Nonadherence to prescribed therapy is a ubiquitous problem in medicine. In chronic diseases, including asthma, diabetes, and hypertension, only 50% of patients take their medication as prescribed more than 80% of the time. The same is true of patients with HIV infection. However, because of the rapid multiplication and mutation rate of HIV and the relatively low potency and short half-life of most antiretrovirals, very high levels of adherence to antiretroviral schedules are necessary to avoid viral resistance. In comparison with patients who are adherent to antiretroviral therapy (ART), nonadherent patients have: 1) Higher mortality (2.5 adjusted relative hazard) (Wood, et al, 2003), 2) Lower increase in CD4 cell count (6 cells/mm³ increase for nonadherent patients versus 83 cells/mm³ increase for adherent patients) (Paterson 2000), and 3) Increased hospital days (12.9 days/1000 days of followup for nonadherent patients versus 2.5 hospital days/1000 days for adherent patients) (Paterson, et al, 2000).

How adherent do patients need to be to avoid viral resistance?

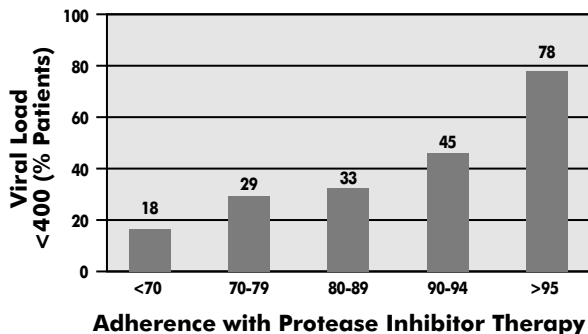
Results of a study of adherence and response to therapy among primarily antiretroviral-experienced patients taking protease inhibitors (PIs) showed that a >95% adherence rate was necessary for 78% of patients to achieve an undetectable viral load (Paterson, 2000); however, some patients with significantly less adherence also had success (see Figure 7-1). Exactly how adherent individual patients need to be is not known and probably depends on several factors, including preexisting antiretroviral resistance, viral load, viral genetic barriers to the development of drug resistance, and drug half-life. Patients should be counseled that the risk of viral resistance increases with nonadherence and that nearly perfect adherence is the goal. Of note, patients with very low levels of adherence may be at decreased risk of developing viral resistance because there is not enough selective pressure (Bangsberg, et al, 2003).

ASSESSMENT

What factors impact adherence?

Many factors contribute to a patient's ability to adhere to medication schedules (Table 7-1). Note that race, education level, and income are generally not predictive of adherence. Providers must remember that factors predicting adherence or nonadherence are only associations and are not absolutely predictive. For example, although patients who use addictive substances are more likely to be nonadherent, some patients with heavy alcohol or drug use are adherent to ART.

Figure 7-1: Adherence Rates Predict Viral Load Response



Source: Adapted from Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133:21-30. Copyright American College of Physicians. modified with permission.

7

One of the primary predictors of adherence is “self-efficacy” or patient readiness. Patients who have confidence in their ability to take their medications as instructed (ie, they have good self-efficacy) are much more likely to be compliant than patients who lack this confidence. Among HIV-infected patients, the common comorbidities of substance abuse and untreated mental illness contribute significantly to nonadherence. Because side effects of the medications also are a significant barrier to patient adherence, providers need to vigorously address complaints of side effects.

What is the best way to assess a patient’s adherence?

There is no gold standard for measuring adherence. A provider’s “impression” of a patients’ adherence, without specific assessments, is very unreliable. Mechanisms to measure adherence include assessment of serum drug levels, electronic monitoring of pill bottle openings, pill counts made at clinic visits or at surprise home visits, pharmacy record reviews, and patient responses to questioning. In general these different measures have good correlations to adherence levels, although asking the patient will be more likely to overestimate adherence than objective measures. Computer-assisted questioning of patients will improve self-reporting reliability. Serum drug level assessment provides only information about the most recent dose and is quite costly and not practical in clinical practice..

Table 7-1: Factors that Promote Patients’ Adherence to Medication Regimens

| Patient-related factors |
|---|
| Absence of mental illness/depression Absence of substance abuse (alcohol and other drugs of abuse) Perceived ability to take medication as instructed (self-efficacy) Older age Higher literacy Strong social support network Adherence with medical appointments Stable housing Adherence with previous therapies Positive attitude toward efficacy of medication |
| Medication-related factors |
| Fewer medications Fewer doses Fewer pills Fewer side effects Lack of dietary restrictions Shorter time on therapy Good “fit” of regimen into patient’s daily routine |
| Health system-related factors |
| Trusting relationship with health care provider Patient education: <ul style="list-style-type: none"> • Patients understand their regimen, including food restrictions • Patients understand the association of adherence and resistance Convenient access to medications and refills |

How should providers ask patients about adherence to get the most reliable information?

With appropriate education at the start of ART, a patient should know the importance of adherence. It is important to approach the discussion of adherence at follow-up visits in a nonjudgmental way and “give permission” for missing doses. Also, asking specific questions will yield specific information. An example of an inquiry might be: “Everyone misses doses of their medication some of the time. How many times in the last 3 days/week/month have you missed taking doses of your medicine?” From there, a discussion of the specific events that led to missing doses can lead to problem-solving with the patient to overcome these barriers.

The provider should ask patients to recount exactly when and how they are taking their medications in order to identify any lack of understanding of the regimen itself or of special dietary instructions.

INTERVENTIONS

What can be done to improve adherence?

The most important intervention is making sure patients start medication only when they are “ready.” Providers need to discuss with patients the risks associated with nonadherence that can result from starting medications before they are ready versus waiting while they “prepare.” Preparing can mean entering into substance abuse treatment, finding stable housing, or attending a support group to overcome fears of medication side effects and concerns about confidentiality. Pregnant women and patients with serious complications of HIV infection and very low CD4 counts may not have the luxury of postponing therapy, but for others, being ready to adhere may be critical to the outcome of ART.

Interventions to improve adherence in chronic diseases tend to have, at best, modest effects on adherence. They are most effective if they are multifaceted, ie, they target several aspects of the adherence behavior and are repeated over time. Barriers to adherence differ among patients. Thus, interventions should be tailored to the patient’s specific needs. In addition, barriers to adherence vary over time, so interventions need to vary as well. Interventions can occur at the level of the provider, care team, clinic, and/or pharmacy. Ideally, interventions are occurring throughout the patient’s medical visit and beyond.

The most commonly used interventions address patient readiness using both one-on-one education and support groups. Peer counseling and support are key for many patients to work through concerns related to medication-taking. Making patients partners in the decisionmaking process about when to start and which regimen to use is also important. The regimen should be as simple as possible and should be the one least likely to cause the side effects that the patient fears the most. Substance abuse and mental illness should be treated *before starting* medication whenever possible.

After the patient begins the regimen, close followup and monitoring of adherence is critical, often through frequent clinic visits during the first weeks of therapy even if other medical interventions are not necessary. Providers should ask patients about adherence and

address barriers to adherence at each followup visit. Providers should be open to changing the regimen if a patient has significant problems with it, whether related to side effects or to scheduling. Patients should be encouraged to use pill boxes and incorporate reminder systems as needed. Various kinds of interventions have been used in HIV and other chronic diseases (see Table 7-2).

What is the role of Directly Observed Therapy (DOT) for medication adherence?

Directly observed therapy (DOT) refers to medical staff supervising patients taking each dose of medication. DOT has increased treatment completion and decreased the resistance rates of tuberculosis therapy. Whether it is feasible in HIV therapy is currently under investigation. A majority of ongoing studies are using modified DOT, with only 1 daily dose of medication observed over the first several months of therapy or during the administration of methadone maintenance therapy. The results of these studies will provide valuable information about the long-term patient acceptability, cost, and efficacy of this approach to improve adherence over the long term.

Table 7-2: Interventions That Have Been Used to Support Adherence in HIV and Other Chronic Diseases

| Intervention | Comments |
|---|---|
| The Patient | |
| Start when patients are ready | For patients with complications of HIV infection, low CD4 cell counts, or pregnancy, the cost-benefit analysis of treatment is different. |
| Treat substance abuse and depression before initiating ART | If there is no antiretroviral emergency, patients with active substance abuse and depression should have these comorbidities addressed before starting an antiretroviral regimen. |
| Engage patients in medication tailoring | Discuss with patients in detail how the medications will fit into their daily routine- ie, when (and if) meals are eaten, what patients do on a daily basis that can be linked to dosing times. |
| Educate (group/individual) regarding: - the regimen - side effects management - consequences of nonadherence | <ul style="list-style-type: none"> - Patient education is essential -- both group and one-on-one. - Involve caretakers and patient support network in educational efforts. - Patients need to know exactly how to take their medication. A daily calendar with pills on it will help a patient visualize the regimen. - Prior to initiating therapy, patients should know which side effects to expect, what they can do to manage them, and when to call the provider. - Patients need to understand the serious consequences of nonadherence and what to do in the event of a late or missed dose. |
| Increase support | Patients should enlist the aid of family and friends to promote their adherence. The HIV health care team can provide support through office visits, home visits, and telephone calls, especially in the early days and weeks of ART. |
| Use skill building exercises | Patients who are concerned about their ability to adhere should use a trial of jellybeans in a pill box to accustom themselves to their pill taking schedule prior to initiating therapy. This may not increase adherence, but it may give patients insight into their adherence and affect their decision to start medications. |
| Address barriers to adherence | <ul style="list-style-type: none"> - Have patients consider when medications are likely to be missed and make plans to decrease these events. - Some patients store a few doses in places where they spend a lot of time, such as at the houses of friends and relatives. |
| Use reminders | <ul style="list-style-type: none"> - Alarm clocks, in the form of watch alarms, pagers, or pill boxes can decrease missed doses due to simply forgetting. - Patients can place medications in locations where they will notice them at dosing times, such on the breakfast table. |
| The Regimen | |
| Simplify as much as possible | <ul style="list-style-type: none"> - Once or twice-a-day regimens are easiest for patients. - Use as few pills and medications as possible. - Try to use regimens than can be followed without regard to food intake. |
| Tailor the regimen to the patient's lifestyle (and not the patient's lifestyle to the regimen) | <ul style="list-style-type: none"> - Ask patients about their daily routine and comfort in taking medications in front of others and at work. - Construct a regimen that works for the patient. |
| Use pill boxes | <ul style="list-style-type: none"> - Use of pill boxes allows patients a mechanism for carrying their daily medication. - Pill boxes allow patients to easily recognize when they have missed taking a dose. |
| Make refills accessible | - Develop policies to allow patients ready access to refills. |
| The Clinician-Patient Relationship | |
| Develop a trusting relationship | - Rarely is initiation of antiretroviral regimens required at the first visit. Invest in the doctor-patient relationship prior to initiating therapy. |
| Ask about adherence | <ul style="list-style-type: none"> - Providers cannot predict adherence; they must ask patients. - Ask in a nonjudgmental way, with a specific time frame, to get good information. - Give permission for missed doses prior to asking. - Ask repetitively over time. |
| Use positive reinforcement | Share viral load and CD4 results and reinforce the relationship to adherence. |
| Listen to the patient | <ul style="list-style-type: none"> -Individualize therapy based on patient preferences regarding fear of specific side effects or specific medication. -Negotiate the regimen with patients. |
| System of Care | |
| Maintain close followup at initiation of regimen | Have telephone, office, or home contact with patients within first few days of therapy to assess for side effects and accurate understanding of regimen. |
| Develop patient education program | <ul style="list-style-type: none"> - Consider using nurses, case managers, pharmacists, and peers in patient education. - Have written materials accessible. |
| Incorporate the adherence message throughout the medical practice | <ul style="list-style-type: none"> - All staff members need to understand and promote the importance of adherence. - Have pill boxes, alarms, and other adherence aids available to patients. |

KEY POINTS

Medication adherence is a significant challenge in all chronic diseases, but is particularly important in ART because of the high levels of adherence that must be maintained to prevent viral resistance.

Patients should not start taking antiretroviral medications until they are ready. Providers should take the time to assess their readiness, conduct interventions to prepare them to begin therapy, and follow them closely once they start.

Interventions to support adherence should be multifaceted and repeated over time. However, interventions have a modest effect on adherence.



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CASES

1.

AR is a 37-year-old woman who uses heroin and cocaine daily and has a CD4 count of 300 cells/mm³ and an HIV viral load of 150,000 copies/mL. Since she was diagnosed with HIV infection 10 years ago she has primarily sought care when acutely ill. She comes to clinic for the first time in 6 months because she has decided to start “the cocktail.”

Question: How do you manage this patient?

Answer:

This patient is not engaged in primary care and is using heroin daily. Although she might be able to adhere to therapy, she probably won't. Beginning ART is reasonable given her CD4 cell count and viral load; however nothing makes it critical to start therapy immediately.

The patient did not agree with her physician's assessment that her substance abuse was a barrier to medical care or medication adherence. She agreed to contract with her physician to start ART after she made 5 consecutive clinic visits. After several attempts at consecutive visits, the patient enrolled in a methadone-based substance abuse treatment program. She began to come regularly to clinic, engaged in in-depth medication education, and eventually started ART. She had good adherence, maintaining an undetectable viral load for 18 months before a drug abuse relapse. When she began to miss doses, she stopped all her medications as instructed and did not develop significant resistance.

2.

DP is a 4-year-old with perinatally-acquired HIV infection. He is taken care of by his maternal great-grandmother, who is also caring for 3 other great-grandchildren. He resists taking ART because of the taste, so that it takes his great-grandmother 30-60 minutes to administer each dose when she can get him to take it. Although she has worked closely with the behavior modification team at the pediatric clinic, the situation has not improved. His viral load and CD4 cell count have not changed significantly on therapy.

Question: What do you do to treat this patient?

Answer:

Given the patient's refusal to take medication, the decision was made to place a g-tube for ease of administration. Within 1 month the viral load was undetectable, and the time to administer medications had decreased to less than 10 minutes per dose. The great-grandmother reported a significant improvement in their relationship and in DP's behavior in a number of domains. Although this may seem extreme, this is an example of individualizing the intervention to the barriers that exist for the patient (Shingadia, et al 2000).

Chapter 8:

Symptom Management

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WORKUP OF SYMPTOMS

MEDICATION-RELATED ISSUES

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KEY POINTS

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WORKUP OF SYMPTOMS

How should you approach the workup of symptoms in patients infected with HIV?

Symptom evaluation in HIV-infected patients must include knowledge of the CD4 count and viral load as well as close attention to the medication list. An opportunistic disease (OD) is an unlikely cause of symptoms in patients with CD4 cell counts $> 200/\text{mm}^3$. Antiretroviral medications are a common cause of HIV-related symptoms.

MEDICATION-RELATED ISSUES

What are the most common symptoms related to antiretroviral medications?

Nausea and diarrhea are the two most common symptoms associated with antiretroviral therapy (ART). Pruritus and skin rashes are also common, especially with nonnucleoside drugs. Lower extremity pain due to neuropathy is seen with didanosine (ddI), stavudine (d4T), and zalcitabine (ddC).

What are the common side effects of each of the antiretroviral drugs?

The different classes of drugs have many similar as well as distinct side effects (see Table 8-1).

What symptoms could be due to life-threatening acute drug reactions?

Symptoms of life-threatening acute drug reactions are not to be missed. A patient with myalgias, nausea, vomiting, diarrhea, abdominal pain, fever, rash, malaise, and extreme fatigue who has started taking abacavir (ABC) within the previous 6 weeks is

probably suffering from an abacavir hypersensitivity reaction. In this case, abacavir should be permanently discontinued. The hypersensitivity reaction occurs in up to 5% of patients starting on abacavir and can lead to hypotension and death if the patient is rechallenged with abacavir. If a patient taking one of the “d-drugs” (didanosine [ddI], zalcitabine [ddC], stavudine [d4T], dapsone [for *Pneumocystis pneumonia* prophylaxis]) has rapid onset of nausea/vomiting and constant, severe abdominal pain in the epigastrium or upper quadrants that radiates to the back, drug-induced pancreatitis is possible. Patients taking a nucleoside (NRTI) who have vague symptoms including nausea, vomiting, abdominal pain, weight loss, malaise, fatigue, dyspnea, or fever must have lactic acidosis with hepatic steatosis ruled out. This occurs 5-13 months after initiating therapy and has a 60% fatality rate. Patients taking nevirapine (NVP) who have fatigue, malaise, nausea, vomiting, jaundice, and right-upper-quadrant abdominal pain could have nevirapine-induced hepatitis. Also, up to half the patients taking nevirapine may have a rash; however, if the rash is moist, involves the mucous membranes, or is extensive with an associated fever, Stevens-Johnson syndrome, which also occurs in patients taking trimethoprim-sulfamethoxazole (TMP/sulfa), must be considered. Severe cases of Stevens-Johnson syndrome, including toxic epidermal necrolysis (TEN), are medical emergencies and must be managed as burn cases. For all drug-induced, life-threatening illnesses, immediate discontinuation of the offending drug is the crucial first step in care.

What are the most important drug interactions that occur with antiretroviral medications?

Drug interactions are frequently the cause of symptoms and must be closely watched for. Not only do antiretroviral drugs react with each other, they react with numerous prescribed drugs and recreational drugs (see Tables 4-8 in the Pocket Guide).

Table 8-1. Side Effects of Antiretroviral Drugs

| Drug | Side effects |
|--|--|
| Nucleosides (NRTIs) | |
| Class effect | Hepatic steatosis/lactic acidosis |
| abacavir (ABC) | Hypersensitivity reaction (nausea, anorexia, fever, rash, dyspnea, cough) |
| didanosine (ddI) | Pancreatitis, peripheral neuropathy, nausea, diarrhea |
| lamivudine (3TC) | Very few side effects |
| stavudine (d4T) | Peripheral neuropathy, pancreatitis |
| tenofovir (TDF) (a nucleotide) | Nausea, vomiting, diarrhea |
| zalcitabine (ddC) | Peripheral neuropathy, mucosal ulcers, pancreatitis |
| zidovudine (AZT) | Anemia, myopathy, headache, nausea |
| emtricitabine (FTC) | Nausea, very few side effects |
| Nonnucleoside reverse transcriptase inhibitors (NNRTIs) | |
| efavirenz (EFV) | Confusion, insomnia, rash, disturbing dreams |
| nevirapine (NVP) | Rash (15%), hepatitis |
| Protease inhibitors (PIs) | |
| Class effect | Hyperglycemia, hyperlipidemia, lipodystrophy, hepatitis |
| amprenavir (APV) | Nausea, diarrhea, rash, paraesthesias |
| atazanavir (ATV) | Elevated bilirubin |
| fosamprenavir (FAPV) | Diarrhea |
| indinavir (IDV) | Nausea, renal sludging, renal stones, increased indirect bilirubin |
| lopinavir+ritonavir (LPV/r or Kaletra) | Nausea, vomiting, diarrhea |
| nelfinavir (NFV) | Diarrhea common (can be limiting) |
| ritonavir (RTV) | Nausea, vomiting, circumoral paraesthesias, hepatitis, taste abnormalities |
| saquinavir (SQV) | Nausea, diarrhea |

What natural products are potentially useful in treating the symptoms of patients with HIV?

Some commonly used complementary medicine treatments are listed in Table 8-2. Ginger for the treatment of nausea is probably the most effective of the natural products for symptom management.

Table 8-2. Complementary Medicine Treatment Options for Various Symptoms

| Problem | Treatment option | Comments |
|---------------------------|------------------|--|
| Nausea | Ginger | Studies have shown possible benefit |
| Hepatitis | Milk thistle | Inconclusive long-term benefit; may inhibit the p450 system |
| Migraine prophylaxis | Riboflavin | Randomized controlled trial showed benefit |
| Immune system dysfunction | Co-enzyme Q | Studies have shown possible benefit in CD4 cell counts but no outcome benefit has been shown |

NAUSEA

What are the important causes of nausea in patients with HIV?

The most common cause of nausea in patients with HIV is medication side effects. Many of the antiretroviral drugs can result in prominent nausea. Full dose ritonavir (RTV) probably causes the most severe and frequent symptoms, but nausea can be seen with all of the protease inhibitors (PIs). Zidovudine (AZT) frequently causes nausea when first taken. Didanosine (ddI), stavudine (d4T), and zalcitabine (ddC) can all cause nausea, or nausea may be an early sign of the pancreatitis these drugs can lead to. All classes of antiretroviral drugs can cause hepatitis, which may present as intense nausea and fatigue. Nevirapine (NVP) and PIs are the most likely to do this, but nucleosides can cause life-threatening lactic acidosis in association with hepatic steatosis. Nausea can be a component of abacavir (ABC) hypersensitivity reaction, usually associated with fever, rash, vomiting, and anorexia. The commonly used antibiotics trimethoprim-sulfamethoxazole (for *Pneumocystis pneumonia* [PCP] prophylaxis) and azithromycin or clarithromycin (for *Mycobacterium avium* complex [MAC] prophylaxis) can cause nausea.

Nonmedication causes to consider include viral hepatitis (acute hepatitis A, B, or C). Nausea is a common feature of cryptococcal meningitis; other sources of increased intracranial pressure such as CNS lymphoma or toxoplasmosis can also present with severe nausea and vomiting.

What are the best options for managing nausea?

If nausea is due to medications, stopping the medication or removing an interacting drug is the best option. Symptomatic therapy with prochlorperazine or metoclopramide may help. A natural product option is ginger, at a dose of 2 grams daily (no more than 4 grams/day). Switching the time of the dose of the offending drug to be taken with food may be helpful.

PULMONARY SYMPTOMS

What are the possible causes of cough in an HIV-infected patient?

The CD4 cell count is crucial information in determining the cause of cough. In patients with CD4 cell counts $> 200/\text{mm}^3$, viral upper respiratory infections, bacterial pneumonia (caused by *S. pneumoniae* or *H. influenzae* most commonly), tuberculosis (TB), and sinusitis with post-nasal drip are all important causes of cough. Bacterial bronchitis is more common in patients with HIV than in non-HIV-infected patients. In patients with low CD4 cell counts ($< 200/\text{mm}^3$) *Pneumocystis carinii* pneumonia must be considered. The risk of PCP is markedly diminished if the patient is taking trimethoprim-sulfamethoxazole for PCP prophylaxis. The cough that occurs with PCP is usually dry and persistent and will usually have been present for several weeks before a patient seeks evaluation. Fungal disease due to cryptococcus, histoplasmosis, or coccidioidomycosis is more common with lower CD4 cell counts.

What workup is appropriate?

In patients with CD4 cell counts $> 200/\text{mm}^3$ the history and physical exam should determine what testing to do. If the patient has a cough but no fever or productive sputum, no dyspnea, and a normal pulmonary exam, then chest x-ray is not necessary. A patient at high risk for TB should have an x-ray if there is a prolonged cough (> 2 - 3 weeks) regardless of CD4 cell count. In a patient with a low CD4 cell count ($< 200/\text{mm}^3$) the possibility of PCP is much more likely and an aggressive approach is warranted; a chest x-ray can begin the workup. If it is normal, then consider obtaining oxygen saturation measurements with ambulation. An individual who has oxygen desaturations should have further workup. For evaluation of suspected PCP see Chapter 9, Management of Opportunistic Diseases.

Are patients infected with HIV at increased risk of developing bacterial pneumonia?

Available data clearly suggest that HIV-infected patients have an increased risk of developing bacterial pneumonia. In the 1993 CDC classification system, recurrent pneumonia (2 or more episodes in 1 year) is defined as a category C (AIDS-indicator) condition. Pneumococcal pneumonia is the most common bacterial pneumonia in persons infected with HIV, and it occurs approximately 10 times more frequently than in persons not infected with HIV. In addition, the development of pneumococcal pneumonia can occur early in the course of HIV disease, before other manifestations of immune suppression. HIV-infected persons with pneumococcal pneumonia have clinical signs and symptoms similar to those in HIV-negative individuals, but they have an approximately 20-fold higher risk of developing pneumococcal bacteremia. Treatment of pneumococcal pneumonia is generally the same in persons with and without HIV infection. Several studies have shown that HIV-infected persons have a slightly increased risk of developing pneumonia caused by *Pseudomonas aeruginosa*.

How common is sinus disease in patients with HIV?

Sinus disease is very common in patients with HIV. The lower the CD4 cell count, the more severe and more widespread (number of sinuses involved) sinusitis is. In patients with lower CD4 cell counts, chronic sinusitis and lack of response to therapy are more common. The most common organisms involved are *Streptococcus pneumoniae*, *Streptococcus viridans*, and *Pseudomonas aeruginosa*. Pseudomonal sinus infections are more common in patients with CD4 cell counts of $< 50/\text{mm}^3$. Fungal (*Aspergillus*) and viral (Cytomegalovirus) sinusitis can occur in patients with CD4 cell counts $< 100/\text{mm}^3$. Aggressive treatment of sinus disease with saline irrigation, antihistamine/decongestant combinations and full-dose nasal steroids is appropriate. Antibiotics should be given for the normal duration for episodes of acute sinusitis (3-6 week course). If antibiotic therapy and aggressive irrigation do not resolve the problem, referral to an ENT specialist for drainage procedures and for consideration of sinus surgery is appropriate.

FATIGUE

What are the common causes of chronic fatigue in patients with HIV?

Fatigue can have a large impact on the quality of a patient's life. Common descriptors of fatigue include tiredness, weakness, lack of energy, sleepiness, and exhaustion. Of the many possible causes of chronic fatigue in patients with HIV, the most common is depression. Other psychosocial causes include stress, anxiety, use of recreational substances, sleep disturbances, domestic abuse, and lack of exercise. ODs must be considered as a possible cause of fatigue in patients with low CD4 cell counts. Other disease states such as anemia, hypothyroidism, hypogonadism, adrenal insufficiency, influenza and other non-opportunistic infections, diabetes, liver disease, and malnutrition can also present as fatigue. Fatigue can be a side effect of ART and other medications commonly taken by patients with HIV. HIV-associated fatigue is a diagnosis of exclusion.

How do you determine the cause of a patient's fatigue?

Ask if the patient is having other symptoms of depression: change in sleep or appetite patterns, depressed mood, anhedonia, agitation or retardation, difficulties with concentration, decreased self-esteem, and suicidal ideation. Take a thorough social history and determine if multiple life stressors are present. Inquire as to how many hours of sleep the patient is getting per night and the number of middle-of-the-night awakenings; ask if the patient feels rested in the morning. Important history questions that help differentiate a physical from a psychological etiology for fatigue are in Table 8-3. Identify any barriers to effective sleep. Ask about the patient's diet and exercise habits, and determine if the patient drinks alcohol or uses recreational drugs, including caffeine. Thoroughly review the patient's medication list and identify any medications, such as certain antiretroviral drugs, beta-blockers, antihistamines, etc., that can be associated with fatigue. Do a complete review of systems and physical exam to elicit other symptoms or signs that may suggest an OD or other disease state. Simple laboratory tests, such as alanine aminotransferase (ALT), blood glucose, thyroid stimulating hormone (TSH), and hematocrit, can help to rule out common diseases that can cause fatigue. Electrolyte abnormalities can suggest adrenal insufficiency. Order other laboratory or diagnostic tests as symptoms and signs direct.

Table 8-3. History Questions to Differentiate Physical from Psychological Causes of Fatigue

| | Psychological cause | Physical cause |
|------------------------|-----------------------------------|---------------------------------------|
| Onset | Often follows problem or conflict | Related to onset of physical ailments |
| Duration | Chronic | Of recent onset |
| Progression | Fluctuates | Increases as disease advances |
| Effect of sleep | Unaffected by sleep | Relieved by sleep |
| Diurnal | Present in morning, may improve | Increases as the day progresses |

NEUROPATHIC PAIN

What is the most common cause of neuropathic pain and paresthesias in patients with HIV?

Distal symmetrical polyneuropathy (DSP) is most commonly caused by antiretroviral drugs. The drugs didanosine (ddl), zalcitabine (ddC), stavudine (d4T) can all cause DSP at high doses. Studies have shown zalcitabine to be the most likely to cause neuropathy at standard doses; concurrent alcohol use or vitamin B12 deficiency may increase risk. HIV-related DSP is less common than drug-induced DSP. The two types of neuropathies present similarly, although onset may be more acute in drug-induced DSP. HIV-related DSP does not appear to respond to viral suppression with ART.

How do you diagnose and treat DSP?

Diagnose drug-related DSP by linking the onset of the symptoms with the initiation of drug therapy. Treat by drug removal; symptoms may worsen temporarily but should regress within several weeks. Residual painful symptoms of DSP may be treated with tricyclic antidepressants, narcotic analgesics, or gabapentin. The topical medication capsaicin may be helpful if the neuropathy is limited to a small surface area.

DERMATOLOGIC SYMPTOMS

How do you manage generalized pruritus in a patient with no cutaneous signs on exam?

If a patient with HIV has generalized pruritus with no obvious cutaneous diagnosis, acute drug reactions such as Stevens-Johnson syndrome, which can be life-threatening, and coexisting systemic illness such as hepatic dysfunction must be ruled out (see Table 8-4 and earlier section on medication-related issues). Order a complete blood count, liver function tests, and blood chemistries. Occasionally, scabies can present with minimal to no cutaneous signs. Pruritus due solely to HIV infection is a diagnosis of exclusion; it can respond to ART. (Symptomatic treatments for generalized pruritus are listed in Table 8-5.) In general, if a clear cause is not identified, xerosis, a common condition in patients with HIV disease, will be the most likely diagnosis. In this case, decreasing the amount of bathing, avoiding dry soaps, using emollient creams, and ceasing scratching are the basis of symptomatic treatment. In addition, general agents such as H-1 antagonists can be used. The best studied of these is hydroxyzine, which offers the benefit of sedation for nocturnal itching.

| Very common | Less common |
|---|--|
| <ul style="list-style-type: none"> • Staphylococcal folliculitis • Xerosis • Atopic dermatitis • Scabies • Psoriasis • Hypersensitivity to insect bites • Drug reactions | <ul style="list-style-type: none"> • HIV-associated pruritus • Eosinophilic folliculitis • Granuloma annulare • Lymphoma • Hepatic failure • Renal failure |

How does scabies manifest differently in HIV-infected persons?

Among HIV-infected persons with mild-to-moderate immune suppression, scabies causes similar clinical manifestations as seen in persons without HIV infection, namely multiple pruritic papular lesions. Treatment consists of applying 30-60 g of 5% permethrin cream to the entire body from the neck down, leaving it on for 8-12 hours, then washing it off, and repeating the entire process one week later. In HIV-infected persons with severe immune suppression (CD4 count of < 100 cells/mm³), an atypical form of scabies known as crusted or "Norwegian" scabies may develop. Crusted scabies is characterized by an enormous number of scabies

mites and manifests as nonpruritic, thick, grayish-white, plaque-like lesions. In severe cases, the large lesions can develop deep fissures. Treatment of crusted scabies consists of ivermectin 200µg/kg orally with a repeat dose a week later.

| Therapy | Comment |
|--|---|
| Prevention of scratching | Scratching causes secondary irritation |
| Lubrication with ointments and creams with a fatty basis | eg, propylene glycol, wax esters |
| Avoidance of histamine induction by heat | eg, bathing in lukewarm or cold water |
| Avoidance of irritating substances | eg, alkaline soaps, wool clothing |
| Antihistamines | The evidence is sparse; watch for side effects |
| Topical agents <ul style="list-style-type: none"> • Coolants • Anesthetic agents | eg, menthol, phenol eg, EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%) |
| Lindane | Empiric treatment for scabies if risk factors |
| UVB therapy | Three times a week, up to 20 treatments for maximal benefit |
| Hypnosis | Studies have demonstrated benefit |

What are the causes and treatments of blisters and cutaneous ulcers in persons with HIV?

Several studies have suggested that HIV-infected persons, when compared with age-matched HIV-negative persons, have an approximately 10-fold increased risk of developing "shingles," a complication resulting from reactivation of varicella-zoster virus. Herpes zoster can occur at any CD4 cell count and thus does not require advanced HIV-related immune suppression. Indeed, the development of herpes zoster may serve as one of the first clinical events prompting an HIV-infected person to seek medical care. Persons with HIV can have more than one episode of herpes zoster. For unknown reasons, HIV-infected persons who start aggressive ART have an increased risk of developing herpes zoster in the 6-month period after starting ART; in this scenario, the herpes zoster does not reflect worsening immunologic function or waning effectiveness of ART.

Because immune-suppressed persons who develop herpes zoster have an increased risk of disseminated herpes zoster, most experts recommend that all HIV-infected persons with zoster receive therapy. As long as the patient has no evidence of disseminated disease, central nervous system disease, or cranial nerve involvement, oral therapy can be used. Therapy for localized dermatomal zoster consists of 7-10 days of oral therapy with valacyclovir (1000 mg tid), acyclovir (800 mg 5x/day), or famciclovir (500 mg tid). In addition, acute zoster-associated pain often requires therapy. Therapy for zoster in HIV-infected persons should not include corticosteroids. No evidence exists to suggest HIV-infected persons have a higher risk of developing post-herpetic neuralgia as a complication of zoster infection.

Among HIV-infected persons with mild or moderate immune suppression (CD4 count > 350 cells/mm³), herpes simplex virus (HSV) infections cause clinical manifestations similar to those in HIV-negative persons, namely self-limited oral or genital lesions that typically appear with vesicular or ulcerated lesions. Recommended therapy for episodic HSV infection consists of either acyclovir 400 mg po tid x 5-10 days, famciclovir 500 mg po bid x 5-10 days, or valacyclovir 1000 mg po bid x 5-10 days. In persons with more advanced immune suppression, particularly those with severe immune suppression (CD4 count < 100 cells/mm³), HSV infection may present as a non-healing, large, ulcerated lesion anywhere on the body. Therapy for these chronic, ulcerated lesions typically requires longer duration. In addition, those HIV-infected persons with severe immune suppression who receive chronic suppressive therapy for HSV have an increased risk of developing acyclovir-resistant HSV infection.

How does molluscum contagiosum manifest in severely immunosuppressed persons with HIV?

Among HIV-infected patients with severe immune suppression (CD4 count < 100 cells/mm³), molluscum contagiosum typically presents as flesh-colored, papular lesions, most often on the face, neck, chest, or genitalia. In contrast to immune competent patients who typically have a self-resolving illness, HIV-infected persons with severe immune suppression generally have a progressive increase in the number and size of the molluscum lesions, often culminating in very large and disfiguring lesions referred to as “giant molluscum.” These lesions are particularly problematic if located on the face. Extremely large lesions may require surgical removal, moderate-sized lesions typically respond to

liquid nitrogen therapy, and multiple small lesions are best treated with topical tretinoin 0.025% applied once a day. In addition, effective ART with improvement in immune function may help in managing molluscum.

How do you recognize and treat seborrheic dermatitis?

Although seborrheic dermatitis is a well-known dermatologic disorder in persons who do not have HIV infection, this disorder occurs with increased frequency and severity among HIV-infected persons. Patients with HIV infection and seborrheic dermatitis typically have symmetrical erythematous, scaled patches and flaking, most often on the scalp, eyebrows, beard, central chest, and axillae. Typically, seborrheic dermatitis spares the central part of the face. Most patients respond to topical antifungal creams, such as 2% ketoconazole cream. In some instances, adding 1% hydrocortisone cream may be required.

MOUTH LESIONS

Many patients with HIV have mouth pain: what are the most common mouth lesions?

The two most common oral lesions in HIV patients are oral candidiasis and oral hairy leukoplakia; they are clinical markers of symptomatic HIV infection. Oral hairy leukoplakia is a raised, white lesion that is usually seen on the lateral surface of the tongue. Hair-like projections can occasionally be visualized. It is usually asymptomatic, but may cause discomfort and impair taste and eating as it grows in size. The lesion appears more frequently in patients with lower CD4 counts and is thought to be caused by the Epstein-Barr virus.

Mucosal *candida* infections are seen as the CD4 cell count falls below 200-300 cells/mm³. The manifestations vary; they can involve the hard and soft palates, buccal mucosa, tongue, pharynx, and hypopharynx. The most common presentation is pseudomembranous candidiasis, or thrush. “Cottage cheese” plaques are seen on the soft palate, tonsils, and buccal mucosa and can be removed with a tongue blade. Atrophic candidiasis is a less seen and underdiagnosed form of candidiasis, consisting of flat, erythematous plaques in the same distribution as pseudomembranous candidiasis but lacking the white exudates. Mouth pain and loss of acuity of taste are common symptoms with atrophic candidiasis.

Diagnosis of a *candida* infection is commonly based on physical exam findings. Examination of a KOH preparation of a plaque scraping may also be used; culturing is rarely necessary. Response to a trial of topical antifungal agents (clotrimazole troches are easier than liquid nystatin to use) establishes the diagnosis. If the above diagnostics do not suggest *Candida*, a biopsy of the lesion may be performed. Oral hairy leukoplakia needs to be treated only if it causes mouth pain. It can be treated with high-dose acyclovir, valacyclovir, or famciclovir.

What are the causes of painful oral ulcers in patients with HIV?

Oral ulcers are common in patients with HIV. HSV causes primary or recurrent small, smooth, painful ulcers on the lips, gums, hard palate, or buccal mucosa. They can present as solitary lesions or in clusters. Lesions often last weeks, and treatment with acyclovir can shorten the course. Patients with disseminated cytomegalovirus (CMV) infection can occasionally have a large, solitary oral lesion. Aphthous stomatitis can present as single or multiple painful ulcers on the buccal and labial mucosa and the lateral aspect of the tongue. Aphthous ulcers are often exudative or necrotic in patients with HIV, and the course is usually more prolonged than in patients without HIV. Drug therapy with zalcitabine (ddC) can also cause ulcers. In managing oral ulcers, biopsy and viral culture establishes the etiology; some suggest treating empirically for HSV. If the lesion is consistent with aphthous ulcers, treat either with topical or oral steroids or thalidomide. An oral suspension consisting of diphenhydramine, viscous lidocaine, tetracycline, and dexamethasone may offer some pain relief. Removal of the offending drug is the treatment for drug-induced ulcers.

How do you recognize and treat gingivitis and periodontal disease?

These diseases can develop either insidiously or abruptly in patients with HIV and may be severe. Gingivitis is common and can occur at any CD4 cell count. Severe pain, foul breath, bleeding gums, and loosening of teeth are common symptoms, and exam may show a bright red marginal line on the gingiva, gingival erosion, necrosis and ulceration of interdental papillae, exfoliation of enamel, and loose teeth. The cause is unclear, although aerobic and anaerobic gram-negative bacteria, spirochetes, and yeast have been implicated. Severe, ulcerating gingivitis can be caused by *Klebsiella pneumoniae*, *Enterobacter*

cloacae, and other gram-negative bacilli. Treatment includes debridement, irrigation with povidone-iodine/chlorhexidine oral solutions, and topical antiseptic agents or metronidazole.

WASTING

What are the common causes of weight loss and wasting in patients with HIV?

There can be many different psychological and physical causes of weight loss in HIV disease (see Table 8-6).

Table 8-6. Common Causes of Weight Loss in Patients with HIV

| |
|---|
| Inadequate dietary intake resulting from |
| Depression |
| Painful oral lesions |
| Esophageal lesions causing dysphagia |
| Reduced taste sensation (thrush/meds) |
| Medication side effects (eg, nausea) |
| Chronic diarrhea (malabsorption) resulting from |
| Cryptosporidia |
| Giardia |
| Hypermetabolic states |
| Infection |
| Occult malignancy (eg, B-cell lymphoma) |
| Endocrine problems |
| Hypogonadism |
| Adrenal insufficiency |
| Diabetes (PI-induced) |

How do you work up a patient with weight loss and wasting?

The workup is driven by results of the history, physical exam, and CD4 cell count; a higher CD4 count is more suggestive of causes such as endocrine disorders, malignancies, depression, or medication side effects. Serum testosterone, glucose, and thyroid tests to assess hormone status may be ordered. If malnutrition is suspected, it is important to address this promptly, since malnutrition decreases the function and number of immunity cells and leads to increased morbidity and mortality. Evaluation of GI function, calculation of caloric intake, estimation of protein and energy requirements, measurement of serum prealbumin, albumin, folate, and vitamin B12, and determination of the extent of lean body mass lost make up a comprehensive nutritional assessment. Body cell

mass can be measured using mid-arm circumference. Specific dietary deficiencies should be addressed, vitamin and mineral supplements should be prescribed, and high-calorie protein-containing foods should be recommended. In the patient with a low CD4 count (< 100 cells/mm³), OIs such as *Mycobacterium avium* complex (MAC), tuberculosis, cytomegalovirus infection, cryptosporidiosis, and *Pneumocystis carinii* pneumonia (PCP) should be ruled out, as well as lymphoma. Order a complete blood count, chemistries, blood cultures, chest x-ray, oximetry, and gastrointestinal biopsies or stool cultures as indicated. Referral to a nutritionist or registered dietician is often helpful. Also see *Health Care and HIV: Nutritional Guide for Providers and Clients* under Suggested Resources for practical assessment tools and algorithms for providers as well as patient handouts.

What are the medical treatment options for AIDS wasting?

If an underlying cause of wasting has been identified, treatment of that cause is the first step in restoring weight. One important factor may be switching to ART that does not cause gastrointestinal/anorexia symptoms preventing food intake. Any infectious process should be identified and treated. For nonspecific AIDS wasting, the mainstay of treatment is nutritional supplementation along with appetite stimulants and antiemetics. Institution of ART and prevention of OIs are important in restoring weight. Human growth hormone has been shown to rebuild lean body mass, although it is expensive and survival advantage is controversial; some recommend that it be reserved for patients who have intractable, unexplained weight loss and require short-term treatment to maintain body cell mass during an acute illness (see Table 8-7 for treatment options).

MYALGIAS

What are some common causes of myalgias in patients with HIV?

HIV can cause an inflammatory myopathy at any stage of infection. Symptoms include slowly progressive, proximal muscle weakness of the extremities with or without myalgias. Myopathy due to zidovudine (AZT) toxicity presents similarly to HIV-associated myopathy, and it may be difficult to distinguish between these two disorders. Zidovudine toxicity occurs usually after several months of therapy (most commonly after 6 or more months of continual therapy). Myopathy or rhabdomyolysis due to HMG coenzyme A reductase

inhibitors (statins) or fibrates are another important concern with HIV-infected patients. Many patients are on these drugs for treatment of hyperlipidemia caused by treatment with PIs. PIs decrease the metabolism of statins, which can increase the chance of toxicity. Moreover, many patients are on both gemfibrozil and a statin, which can interact to increase the risk of muscle toxicity. Simple myalgias are more common than rhabdomyolysis or myopathy caused by the statins.

Table 8-7. Treatment Options for Specific Causes of Weight Loss

| Cause of weight loss | Treatment options | Comments |
|----------------------|--|--|
| Anorexia | Appetite stimulants <ul style="list-style-type: none"> • dronabinol 2.5-5 mg/d • megestrol acetate 800 mg/d | Some studies show that weight gained is from body fat and not lean body stores. Megestrol can raise blood sugar levels, especially when used with protease inhibitors. |
| Hypogonadism | testosterone <ul style="list-style-type: none"> • IM 200-300 mg every 2-3 weeks • Transdermally <ul style="list-style-type: none"> - Patch 5 mg/day - 1% gel 5-10 g/day oxandrolone nandrolone | Liver function tests must be monitored with use of oral anabolic agents. |

How do you evaluate and manage a patient with myalgias or myopathy?

The first step is to check creatinine phosphokinase (CPK) levels. This should be done for any patient on zidovudine (AZT) or a statin who has symptoms of myalgias or muscle weakness. Periodic (every 3-6 months) monitoring of CPK levels is appropriate for patients who are on a statin/PI or statin/gemfibrozil combination. Muscle biopsy should be performed if signs and symptoms of myopathy do not remit within about a month after drug removal or if a patient has muscle enzyme elevations and is not on a drug known to cause muscle damage. Organisms may be seen on muscle biopsy, indicating an infectious myopathy. If no organisms are seen and there are signs of inflammation on biopsy, an inflammatory myopathy secondary to HIV is likely, and a trial of corticosteroids or therapy with intravenous immune globulin (IVIG) should be implemented.

DIARRHEA

What are the common causes of diarrhea in patients with HIV?

The main causes of diarrhea are related to either infections or medications. Infectious diarrhea can be caused by a number of organisms, dependent on the patient's CD4 cell count (see Table 8-8). Nelfinavir (NFV) is the antiretroviral drug most commonly associated with diarrhea. All the PIs can cause diarrhea. Didanosine (ddI) is the nucleoside most associated with diarrhea, but diarrhea is less common when the enteric coated (EC) form is used. Metformin, a drug used for treatment of lipodystrophy syndrome and diabetes, commonly causes diarrhea.

| Table 8-8. Infectious Causes of Diarrhea in Patients with HIV |
|--|
| Any CD4 cell count (acute diarrhea) |
| Viruses (especially Norwalk virus) |
| <i>Clostridium difficile</i> (previous antibiotic exposure) |
| <i>Salmonella</i> spp |
| <i>Shigella</i> spp |
| <i>Campylobacter</i> spp |
| Any CD4 cell count (chronic diarrhea) |
| <i>Clostridium difficile</i> |
| <i>Giardia lamblia</i> |
| CD4 count <300 cells/mm³ (chronic diarrhea) |
| Microsporidia |
| Cryptosporidia |
| <i>Mycobacterium avium</i> complex (CD4<100) |
| <i>Isospora belli</i> |
| Cytomegalovirus (CD4 count <100/mm ³) |
| Idiopathic |

What is the best approach to the evaluation of chronic diarrhea in the patient with HIV?

For patients who are on medication that can cause intractable diarrhea, one option is a trial of antidiarrheal medications (loperamide or atropine/phenoxylate either alone or in combination) and continuation of the previous antiretroviral regimen. If this does not work, another option is a trial off medication. If a patient is on ART, stop all medications for the 1-week evaluation

period. If there is a response, then a new agent can be substituted for the most likely causative drug, usually nelfinavir (NFV) or lopinavir plus ritonavir (LPV/r, or Kaletra). If there is no response when medications are stopped, then stool studies should be done. If the patient has a high CD4 cell count (> 300/mm³), start with *C. difficile* toxin and *Giardia* antigen. If the CD4 cell count is low (< 300/mm³), do a full workup with *C. difficile*, *Giardia* antigen, *Microsporidia*/*Cryptosporidia* assay, and modified AFB stain for cryptosporidia. If no organisms are identified, in patients with very low CD4 cell counts (< 100/mm³) obtain blood cultures for *Mycobacterium avium*, and if these are negative, pursue lower endoscopy with particular emphasis on detection of cytomegalovirus on biopsy. In patients with higher CD4 cell counts, clinical followup and trials of antimotility drugs are a reasonable approach before pursuing endoscopy.

HEADACHE

What are the important causes of headaches in HIV-infected patients?

The causes of headache vary according to CD4 cell count. Patients with a CD4 count of > 300 cells/mm³ usually have headaches with common causes such as muscle tension, migraine, or drug side effect. Sinusitis is more frequent in patients with than without HIV and may cause headaches. In patients with low CD4 counts (< 200 cells/mm³) opportunistic infections (eg, Cryptococcal meningitis, toxoplasmic encephalitis) and malignancies (eg, CNS lymphoma) are important causes to consider.

How should you work up patients with headache?

Patients with CD4 counts of < 200 cells/mm³ should have a contrast head CT scan or MRI, followed by lumbar puncture if the scan does not reveal a cause. In a study of CT scans for evaluation of headaches in HIV-positive patients all cases with mass lesions or white-matter lesions occurred in patients with CD4 counts of < 200 cells/mm³. Serologic tests for cryptococcal antigen and *Toxoplasma* titers are helpful in patients with CD4 counts of < 200 cells/mm³.

KEY POINTS

Antiretroviral medications are a common cause of HIV-related symptoms. Some drugs can cause life-threatening reactions and conditions, including hypersensitivity reaction, pancreatitis, lactic acidosis, and Stevens-Johnson syndrome.

The CD4 cell count and viral load are important in symptom evaluation; symptoms associated with OIs in immunocompromised patients have other causes in patients with intact immune function.

Nausea and diarrhea, very common side effects of PIs, zidovudine, and didanosine, can be managed by switching drugs or with symptomatic therapy.

Pneumococcal pneumonia, the most common bacterial pneumonia in persons with HIV, can occur early in the course of the disease, before other manifestations of immune suppression. Sinus disease is also common in persons with HIV.

Chronic fatigue requires a careful assessment to differentiate psychological from physical etiologies so that the underlying cause can be addressed.

Painful neuropathy, frequently caused by antiretroviral medications, can also result from HIV disease. Treatment may include stopping a drug or treating with tricyclic antidepressants, narcotic analgesics, or gabapentin.

Dermatologic problems common in HIV disease include pruritus, crusted scabies, herpes zoster, molluscum contagiosum, and seborrheic dermatitis.

Common oral lesions include oral candidiasis, oral hairy leukoplakia, ulcers, and gingivitis. Common causes of oral ulcers are zalcitabine, HSV, and aphthous ulcers.

Wasting may have a treatable cause, but even nonspecific AIDS wasting can be treated with nutritional supplementation, appetite stimulants and antiemetics.

Myalgia, an especially common side effect of taking a PI and a statin, may require muscle biopsy and treatment with either an antibiotic or IVIG or steroids if the condition does not improve after stopping the implicated medications.

Headaches, common with HIV disease, may be due to a CNS infection or neoplasm if the CD4 count is less than 200 cells/mm³.



SUGGESTED RESOURCES

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CASES

1.

A 45-year-old HIV-positive man, last CD4 count 150 cells/mm³, comes to see you reporting aching in his right arm for 3 weeks. It began with only mild tenderness, but in the last week has become more painful and seems swollen. He is on ART with zidovudine (AZT), efavirenz (EFV), and nelfinavir (NFV). He is taking atorvastatin for hyperlipidemia. On physical exam, he is febrile, and his right arm is edematous and radiating heat without erythema. You obtain a CPK level which is normal.

Question: What is the most likely diagnosis?

Answer:

This patient has symptoms and signs of infectious myositis or pyomyositis, which usually develops insidiously over 2-3 weeks. In the first phase of infection, the involved muscle is tender with mild swelling. After 2-3 weeks a second phase manifests, usually with fever and edema, heat, and painful induration of the involved muscle. Erythema over the muscle is usually not seen. Laboratory values are usually notable for a lower than expected CPK but may include an elevated sedimentation rate and leukocytosis. Zidovudine-induced, statin-induced, and HIV-associated myopathy are less likely, as CPK would be elevated in these disorders, and the symptoms and signs in this patient are localized to one muscle group. Confirm the diagnosis of infectious myopathy with ultrasound or CT or MRI scanning, which will show a purulent abscess in the involved muscle. Blood cultures are not useful. If not treated, septic shock often ensues.

Question: What is the most likely cause?

Answer:

Most cases of infectious myositis are due to infection with *Staphylococcal aureus*. Other organisms reported have included *Streptococcus*, *Toxoplasma gondii*, cytomegalovirus, *Microsporidia*, *Cryptococcus neoformans*, *Mycobacterium avium intracellulare*, *Salmonella*, *Nocardia*, and gram-negative organisms.

2.

A 37-year-old man with Category 3 HIV disease (an AIDS indicator condition plus CD4 count nadir of <200 cells/mm³), last CD4 count 350 cells/mm³, comes to your office complaining of fatigue, nonspecific abdominal pain, nausea, and vomiting for the past 12 days. Review of systems is otherwise negative. He takes stavudine (d4T), zidovudine (AZT), and nelfinavir (NFV) as ART and fluoxetine for depression. On physical exam, his temperature is 37.9 degrees, respiratory rate is 25, abdomen is diffusely mildly tender to palpation, with increased tenderness in the right upper quadrant, no signs of jaundice, guaiac is negative.

Question: What is the differential diagnosis of causes related to ART?

Answer:

The differential diagnosis of ART-related etiologies in this case should include pancreatitis, based on symptoms of abdominal pain, nausea, and vomiting in a patient taking stavudine, although pancreatitis usually presents more acutely with more severe pain. Hepatitis should be considered with these symptoms in patients taking PIs. Lactic acidosis should always be suspected in a patient with these symptoms taking a nucleoside.

Question: What initial lab work should be ordered?

Answer:

Initial lab work may include CBC, basic metabolic panel, liver panel, amylase, lipase, lactate level, and coagulation studies. In the case of this patient, the lactic acid level was elevated. Further support for the diagnosis of lactic acidosis would include an increased anion gap, decreased bicarbonate, and elevated aminotransferases, lipase, amylase, CPK, and LDH.

Chapter 8:

Symptom Management

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WORKUP OF SYMPTOMS

MEDICATION-RELATED ISSUES

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PULMONARY SYMPTOMS

FATIGUE

NEUROPATHIC PAIN

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MOUTH LESIONS

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CASES

WORKUP OF SYMPTOMS

How should you approach the workup of symptoms in patients infected with HIV?

Symptom evaluation in HIV-infected patients must include knowledge of the CD4 count and viral load as well as close attention to the medication list. An opportunistic disease (OD) is an unlikely cause of symptoms in patients with CD4 cell counts $> 200/\text{mm}^3$. Antiretroviral medications are a common cause of HIV-related symptoms.

MEDICATION-RELATED ISSUES

What are the most common symptoms related to antiretroviral medications?

Nausea and diarrhea are the two most common symptoms associated with antiretroviral therapy (ART). Pruritus and skin rashes are also common, especially with nonnucleoside drugs. Lower extremity pain due to neuropathy is seen with didanosine (ddI), stavudine (d4T), and zalcitabine (ddC).

What are the common side effects of each of the antiretroviral drugs?

The different classes of drugs have many similar as well as distinct side effects (see Table 8-1).

What symptoms could be due to life-threatening acute drug reactions?

Symptoms of life-threatening acute drug reactions are not to be missed. A patient with myalgias, nausea, vomiting, diarrhea, abdominal pain, fever, rash, malaise, and extreme fatigue who has started taking abacavir (ABC) within the previous 6 weeks is

probably suffering from an abacavir hypersensitivity reaction. In this case, abacavir should be permanently discontinued. The hypersensitivity reaction occurs in up to 5% of patients starting on abacavir and can lead to hypotension and death if the patient is rechallenged with abacavir. If a patient taking one of the “d-drugs” (didanosine [ddI], zalcitabine [ddC], stavudine [d4T], dapsone [for *Pneumocystis pneumonia* prophylaxis]) has rapid onset of nausea/vomiting and constant, severe abdominal pain in the epigastrium or upper quadrants that radiates to the back, drug-induced pancreatitis is possible. Patients taking a nucleoside (NRTI) who have vague symptoms including nausea, vomiting, abdominal pain, weight loss, malaise, fatigue, dyspnea, or fever must have lactic acidosis with hepatic steatosis ruled out. This occurs 5-13 months after initiating therapy and has a 60% fatality rate. Patients taking nevirapine (NVP) who have fatigue, malaise, nausea, vomiting, jaundice, and right-upper-quadrant abdominal pain could have nevirapine-induced hepatitis. Also, up to half the patients taking nevirapine may have a rash; however, if the rash is moist, involves the mucous membranes, or is extensive with an associated fever, Stevens-Johnson syndrome, which also occurs in patients taking trimethoprim-sulfamethoxazole (TMP/sulfa), must be considered. Severe cases of Stevens-Johnson syndrome, including toxic epidermal necrolysis (TEN), are medical emergencies and must be managed as burn cases. For all drug-induced, life-threatening illnesses, immediate discontinuation of the offending drug is the crucial first step in care.

What are the most important drug interactions that occur with antiretroviral medications?

Drug interactions are frequently the cause of symptoms and must be closely watched for. Not only do antiretroviral drugs react with each other, they react with numerous prescribed drugs and recreational drugs (see Tables 4-8 in the Pocket Guide).

Table 8-1. Side Effects of Antiretroviral Drugs

| Drug | Side effects |
|--|--|
| Nucleosides (NRTIs) | |
| Class effect | Hepatic steatosis/lactic acidosis |
| abacavir (ABC) | Hypersensitivity reaction (nausea, anorexia, fever, rash, dyspnea, cough) |
| didanosine (ddI) | Pancreatitis, peripheral neuropathy, nausea, diarrhea |
| lamivudine (3TC) | Very few side effects |
| stavudine (d4T) | Peripheral neuropathy, pancreatitis |
| tenofovir (TDF) (a nucleotide) | Nausea, vomiting, diarrhea |
| zalcitabine (ddC) | Peripheral neuropathy, mucosal ulcers, pancreatitis |
| zidovudine (AZT) | Anemia, myopathy, headache, nausea |
| emtricitabine (FTC) | Nausea, very few side effects |
| Nonnucleoside reverse transcriptase inhibitors (NNRTIs) | |
| efavirenz (EFV) | Confusion, insomnia, rash, disturbing dreams |
| nevirapine (NVP) | Rash (15%), hepatitis |
| Protease inhibitors (PIs) | |
| Class effect | Hyperglycemia, hyperlipidemia, lipodystrophy, hepatitis |
| amprenavir (APV) | Nausea, diarrhea, rash, paraesthesias |
| atazanavir (ATV) | Elevated bilirubin |
| fosamprenavir (FAPV) | Diarrhea |
| indinavir (IDV) | Nausea, renal sludging, renal stones, increased indirect bilirubin |
| lopinavir+ritonavir (LPV/r or Kaletra) | Nausea, vomiting, diarrhea |
| nelfinavir (NFV) | Diarrhea common (can be limiting) |
| ritonavir (RTV) | Nausea, vomiting, circumoral paraesthesias, hepatitis, taste abnormalities |
| saquinavir (SQV) | Nausea, diarrhea |

What natural products are potentially useful in treating the symptoms of patients with HIV?

Some commonly used complementary medicine treatments are listed in Table 8-2. Ginger for the treatment of nausea is probably the most effective of the natural products for symptom management.

Table 8-2. Complementary Medicine Treatment Options for Various Symptoms

| Problem | Treatment option | Comments |
|---------------------------|------------------|--|
| Nausea | Ginger | Studies have shown possible benefit |
| Hepatitis | Milk thistle | Inconclusive long-term benefit; may inhibit the p450 system |
| Migraine prophylaxis | Riboflavin | Randomized controlled trial showed benefit |
| Immune system dysfunction | Co-enzyme Q | Studies have shown possible benefit in CD4 cell counts but no outcome benefit has been shown |

NAUSEA

What are the important causes of nausea in patients with HIV?

The most common cause of nausea in patients with HIV is medication side effects. Many of the antiretroviral drugs can result in prominent nausea. Full dose ritonavir (RTV) probably causes the most severe and frequent symptoms, but nausea can be seen with all of the protease inhibitors (PIs). Zidovudine (AZT) frequently causes nausea when first taken. Didanosine (ddI), stavudine (d4T), and zalcitabine (ddC) can all cause nausea, or nausea may be an early sign of the pancreatitis these drugs can lead to. All classes of antiretroviral drugs can cause hepatitis, which may present as intense nausea and fatigue. Nevirapine (NVP) and PIs are the most likely to do this, but nucleosides can cause life-threatening lactic acidosis in association with hepatic steatosis. Nausea can be a component of abacavir (ABC) hypersensitivity reaction, usually associated with fever, rash, vomiting, and anorexia. The commonly used antibiotics trimethoprim-sulfamethoxazole (for *Pneumocystis pneumonia* [PCP] prophylaxis) and azithromycin or clarithromycin (for *Mycobacterium avium* complex [MAC] prophylaxis) can cause nausea.

Nonmedication causes to consider include viral hepatitis (acute hepatitis A, B, or C). Nausea is a common feature of cryptococcal meningitis; other sources of increased intracranial pressure such as CNS lymphoma or toxoplasmosis can also present with severe nausea and vomiting.

What are the best options for managing nausea?

If nausea is due to medications, stopping the medication or removing an interacting drug is the best option. Symptomatic therapy with prochlorperazine or metoclopramide may help. A natural product option is ginger, at a dose of 2 grams daily (no more than 4 grams/day). Switching the time of the dose of the offending drug to be taken with food may be helpful.

PULMONARY SYMPTOMS

What are the possible causes of cough in an HIV-infected patient?

The CD4 cell count is crucial information in determining the cause of cough. In patients with CD4 cell counts $> 200/\text{mm}^3$, viral upper respiratory infections, bacterial pneumonia (caused by *S. pneumoniae* or *H. influenzae* most commonly), tuberculosis (TB), and sinusitis with post-nasal drip are all important causes of cough. Bacterial bronchitis is more common in patients with HIV than in non-HIV-infected patients. In patients with low CD4 cell counts ($< 200/\text{mm}^3$) *Pneumocystis carinii* pneumonia must be considered. The risk of PCP is markedly diminished if the patient is taking trimethoprim-sulfamethoxazole for PCP prophylaxis. The cough that occurs with PCP is usually dry and persistent and will usually have been present for several weeks before a patient seeks evaluation. Fungal disease due to cryptococcus, histoplasmosis, or coccidioidomycosis is more common with lower CD4 cell counts.

What workup is appropriate?

In patients with CD4 cell counts $> 200/\text{mm}^3$ the history and physical exam should determine what testing to do. If the patient has a cough but no fever or productive sputum, no dyspnea, and a normal pulmonary exam, then chest x-ray is not necessary. A patient at high risk for TB should have an x-ray if there is a prolonged cough ($> 2-3$ weeks) regardless of CD4 cell count. In a patient with a low CD4 cell count ($< 200/\text{mm}^3$) the possibility of PCP is much more likely and an aggressive approach is warranted; a chest x-ray can begin the workup. If it is normal, then consider obtaining oxygen saturation measurements with ambulation. An individual who has oxygen desaturations should have further workup. For evaluation of suspected PCP see Chapter 9, Management of Opportunistic Diseases.

Are patients infected with HIV at increased risk of developing bacterial pneumonia?

Available data clearly suggest that HIV-infected patients have an increased risk of developing bacterial pneumonia. In the 1993 CDC classification system, recurrent pneumonia (2 or more episodes in 1 year) is defined as a category C (AIDS-indicator) condition. Pneumococcal pneumonia is the most common bacterial pneumonia in persons infected with HIV, and it occurs approximately 10 times more frequently than in persons not infected with HIV. In addition, the development of pneumococcal pneumonia can occur early in the course of HIV disease, before other manifestations of immune suppression. HIV-infected persons with pneumococcal pneumonia have clinical signs and symptoms similar to those in HIV-negative individuals, but they have an approximately 20-fold higher risk of developing pneumococcal bacteremia. Treatment of pneumococcal pneumonia is generally the same in persons with and without HIV infection. Several studies have shown that HIV-infected persons have a slightly increased risk of developing pneumonia caused by *Pseudomonas aeruginosa*.

How common is sinus disease in patients with HIV?

Sinus disease is very common in patients with HIV. The lower the CD4 cell count, the more severe and more widespread (number of sinuses involved) sinusitis is. In patients with lower CD4 cell counts, chronic sinusitis and lack of response to therapy are more common. The most common organisms involved are *Streptococcus pneumoniae*, *Streptococcus viridans*, and *Pseudomonas aeruginosa*. Pseudomonal sinus infections are more common in patients with CD4 cell counts of $< 50/\text{mm}^3$. Fungal (*Aspergillus*) and viral (Cytomegalovirus) sinusitis can occur in patients with CD4 cell counts $< 100/\text{mm}^3$. Aggressive treatment of sinus disease with saline irrigation, antihistamine/decongestant combinations and full-dose nasal steroids is appropriate. Antibiotics should be given for the normal duration for episodes of acute sinusitis (3-6 week course). If antibiotic therapy and aggressive irrigation do not resolve the problem, referral to an ENT specialist for drainage procedures and for consideration of sinus surgery is appropriate.

FATIGUE

What are the common causes of chronic fatigue in patients with HIV?

Fatigue can have a large impact on the quality of a patient's life. Common descriptors of fatigue include tiredness, weakness, lack of energy, sleepiness, and exhaustion. Of the many possible causes of chronic fatigue in patients with HIV, the most common is depression. Other psychosocial causes include stress, anxiety, use of recreational substances, sleep disturbances, domestic abuse, and lack of exercise. ODs must be considered as a possible cause of fatigue in patients with low CD4 cell counts. Other disease states such as anemia, hypothyroidism, hypogonadism, adrenal insufficiency, influenza and other non-opportunistic infections, diabetes, liver disease, and malnutrition can also present as fatigue. Fatigue can be a side effect of ART and other medications commonly taken by patients with HIV. HIV-associated fatigue is a diagnosis of exclusion.

How do you determine the cause of a patient's fatigue?

Ask if the patient is having other symptoms of depression: change in sleep or appetite patterns, depressed mood, anhedonia, agitation or retardation, difficulties with concentration, decreased self-esteem, and suicidal ideation. Take a thorough social history and determine if multiple life stressors are present. Inquire as to how many hours of sleep the patient is getting per night and the number of middle-of-the-night awakenings; ask if the patient feels rested in the morning. Important history questions that help differentiate a physical from a psychological etiology for fatigue are in Table 8-3. Identify any barriers to effective sleep. Ask about the patient's diet and exercise habits, and determine if the patient drinks alcohol or uses recreational drugs, including caffeine. Thoroughly review the patient's medication list and identify any medications, such as certain antiretroviral drugs, beta-blockers, antihistamines, etc., that can be associated with fatigue. Do a complete review of systems and physical exam to elicit other symptoms or signs that may suggest an OD or other disease state. Simple laboratory tests, such as alanine aminotransferase (ALT), blood glucose, thyroid stimulating hormone (TSH), and hematocrit, can help to rule out common diseases that can cause fatigue. Electrolyte abnormalities can suggest adrenal insufficiency. Order other laboratory or diagnostic tests as symptoms and signs direct.

Table 8-3. History Questions to Differentiate Physical from Psychological Causes of Fatigue

| | Psychological cause | Physical cause |
|------------------------|-----------------------------------|---------------------------------------|
| Onset | Often follows problem or conflict | Related to onset of physical ailments |
| Duration | Chronic | Of recent onset |
| Progression | Fluctuates | Increases as disease advances |
| Effect of sleep | Unaffected by sleep | Relieved by sleep |
| Diurnal | Present in morning, may improve | Increases as the day progresses |

NEUROPATHIC PAIN

What is the most common cause of neuropathic pain and paresthesias in patients with HIV?

Distal symmetrical polyneuropathy (DSP) is most commonly caused by antiretroviral drugs. The drugs didanosine (ddl), zalcitabine (ddC), stavudine (d4T) can all cause DSP at high doses. Studies have shown zalcitabine to be the most likely to cause neuropathy at standard doses; concurrent alcohol use or vitamin B12 deficiency may increase risk. HIV-related DSP is less common than drug-induced DSP. The two types of neuropathies present similarly, although onset may be more acute in drug-induced DSP. HIV-related DSP does not appear to respond to viral suppression with ART.

How do you diagnose and treat DSP?

Diagnose drug-related DSP by linking the onset of the symptoms with the initiation of drug therapy. Treat by drug removal; symptoms may worsen temporarily but should regress within several weeks. Residual painful symptoms of DSP may be treated with tricyclic antidepressants, narcotic analgesics, or gabapentin. The topical medication capsaicin may be helpful if the neuropathy is limited to a small surface area.

DERMATOLOGIC SYMPTOMS

How do you manage generalized pruritus in a patient with no cutaneous signs on exam?

If a patient with HIV has generalized pruritus with no obvious cutaneous diagnosis, acute drug reactions such as Stevens-Johnson syndrome, which can be life-threatening, and coexisting systemic illness such as hepatic dysfunction must be ruled out (see Table 8-4 and earlier section on medication-related issues). Order a complete blood count, liver function tests, and blood chemistries. Occasionally, scabies can present with minimal to no cutaneous signs. Pruritus due solely to HIV infection is a diagnosis of exclusion; it can respond to ART. (Symptomatic treatments for generalized pruritus are listed in Table 8-5.) In general, if a clear cause is not identified, xerosis, a common condition in patients with HIV disease, will be the most likely diagnosis. In this case, decreasing the amount of bathing, avoiding dry soaps, using emollient creams, and ceasing scratching are the basis of symptomatic treatment. In addition, general agents such as H-1 antagonists can be used. The best studied of these is hydroxyzine, which offers the benefit of sedation for nocturnal itching.

| Very common | Less common |
|---|--|
| <ul style="list-style-type: none"> • Staphylococcal folliculitis • Xerosis • Atopic dermatitis • Scabies • Psoriasis • Hypersensitivity to insect bites • Drug reactions | <ul style="list-style-type: none"> • HIV-associated pruritus • Eosinophilic folliculitis • Granuloma annulare • Lymphoma • Hepatic failure • Renal failure |

How does scabies manifest differently in HIV-infected persons?

Among HIV-infected persons with mild-to-moderate immune suppression, scabies causes similar clinical manifestations as seen in persons without HIV infection, namely multiple pruritic papular lesions. Treatment consists of applying 30-60 g of 5% permethrin cream to the entire body from the neck down, leaving it on for 8-12 hours, then washing it off, and repeating the entire process one week later. In HIV-infected persons with severe immune suppression (CD4 count of < 100 cells/mm³), an atypical form of scabies known as crusted or "Norwegian" scabies may develop. Crusted scabies is characterized by an enormous number of scabies

mites and manifests as nonpruritic, thick, grayish-white, plaque-like lesions. In severe cases, the large lesions can develop deep fissures. Treatment of crusted scabies consists of ivermectin 200µg/kg orally with a repeat dose a week later.

| Therapy | Comment |
|--|---|
| Prevention of scratching | Scratching causes secondary irritation |
| Lubrication with ointments and creams with a fatty basis | eg, propylene glycol, wax esters |
| Avoidance of histamine induction by heat | eg, bathing in lukewarm or cold water |
| Avoidance of irritating substances | eg, alkaline soaps, wool clothing |
| Antihistamines | The evidence is sparse; watch for side effects |
| Topical agents <ul style="list-style-type: none"> • Coolants • Anesthetic agents | eg, menthol, phenol eg, EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%) |
| Lindane | Empiric treatment for scabies if risk factors |
| UVB therapy | Three times a week, up to 20 treatments for maximal benefit |
| Hypnosis | Studies have demonstrated benefit |

What are the causes and treatments of blisters and cutaneous ulcers in persons with HIV?

Several studies have suggested that HIV-infected persons, when compared with age-matched HIV-negative persons, have an approximately 10-fold increased risk of developing "shingles," a complication resulting from reactivation of varicella-zoster virus. Herpes zoster can occur at any CD4 cell count and thus does not require advanced HIV-related immune suppression. Indeed, the development of herpes zoster may serve as one of the first clinical events prompting an HIV-infected person to seek medical care. Persons with HIV can have more than one episode of herpes zoster. For unknown reasons, HIV-infected persons who start aggressive ART have an increased risk of developing herpes zoster in the 6-month period after starting ART; in this scenario, the herpes zoster does not reflect worsening immunologic function or waning effectiveness of ART.

Because immune-suppressed persons who develop herpes zoster have an increased risk of disseminated herpes zoster, most experts recommend that all HIV-infected persons with zoster receive therapy. As long as the patient has no evidence of disseminated disease, central nervous system disease, or cranial nerve involvement, oral therapy can be used. Therapy for localized dermatomal zoster consists of 7-10 days of oral therapy with valacyclovir (1000 mg tid), acyclovir (800 mg 5x/day), or famciclovir (500 mg tid). In addition, acute zoster-associated pain often requires therapy. Therapy for zoster in HIV-infected persons should not include corticosteroids. No evidence exists to suggest HIV-infected persons have a higher risk of developing post-herpetic neuralgia as a complication of zoster infection.

Among HIV-infected persons with mild or moderate immune suppression (CD4 count > 350 cells/mm³), herpes simplex virus (HSV) infections cause clinical manifestations similar to those in HIV-negative persons, namely self-limited oral or genital lesions that typically appear with vesicular or ulcerated lesions. Recommended therapy for episodic HSV infection consists of either acyclovir 400 mg po tid x 5-10 days, famciclovir 500 mg po bid x 5-10 days, or valacyclovir 1000 mg po bid x 5-10 days. In persons with more advanced immune suppression, particularly those with severe immune suppression (CD4 count < 100 cells/mm³), HSV infection may present as a non-healing, large, ulcerated lesion anywhere on the body. Therapy for these chronic, ulcerated lesions typically requires longer duration. In addition, those HIV-infected persons with severe immune suppression who receive chronic suppressive therapy for HSV have an increased risk of developing acyclovir-resistant HSV infection.

How does molluscum contagiosum manifest in severely immunosuppressed persons with HIV?

Among HIV-infected patients with severe immune suppression (CD4 count < 100 cells/mm³), molluscum contagiosum typically presents as flesh-colored, papular lesions, most often on the face, neck, chest, or genitalia. In contrast to immune competent patients who typically have a self-resolving illness, HIV-infected persons with severe immune suppression generally have a progressive increase in the number and size of the molluscum lesions, often culminating in very large and disfiguring lesions referred to as “giant molluscum.” These lesions are particularly problematic if located on the face. Extremely large lesions may require surgical removal, moderate-sized lesions typically respond to

liquid nitrogen therapy, and multiple small lesions are best treated with topical tretinoin 0.025% applied once a day. In addition, effective ART with improvement in immune function may help in managing molluscum.

How do you recognize and treat seborrheic dermatitis?

Although seborrheic dermatitis is a well-known dermatologic disorder in persons who do not have HIV infection, this disorder occurs with increased frequency and severity among HIV-infected persons. Patients with HIV infection and seborrheic dermatitis typically have symmetrical erythematous, scaled patches and flaking, most often on the scalp, eyebrows, beard, central chest, and axillae. Typically, seborrheic dermatitis spares the central part of the face. Most patients respond to topical antifungal creams, such as 2% ketoconazole cream. In some instances, adding 1% hydrocortisone cream may be required.

MOUTH LESIONS

Many patients with HIV have mouth pain: what are the most common mouth lesions?

The two most common oral lesions in HIV patients are oral candidiasis and oral hairy leukoplakia; they are clinical markers of symptomatic HIV infection. Oral hairy leukoplakia is a raised, white lesion that is usually seen on the lateral surface of the tongue. Hair-like projections can occasionally be visualized. It is usually asymptomatic, but may cause discomfort and impair taste and eating as it grows in size. The lesion appears more frequently in patients with lower CD4 counts and is thought to be caused by the Epstein-Barr virus.

Mucosal *candida* infections are seen as the CD4 cell count falls below 200-300 cells/mm³. The manifestations vary; they can involve the hard and soft palates, buccal mucosa, tongue, pharynx, and hypopharynx. The most common presentation is pseudomembranous candidiasis, or thrush. “Cottage cheese” plaques are seen on the soft palate, tonsils, and buccal mucosa and can be removed with a tongue blade. Atrophic candidiasis is a less seen and underdiagnosed form of candidiasis, consisting of flat, erythematous plaques in the same distribution as pseudomembranous candidiasis but lacking the white exudates. Mouth pain and loss of acuity of taste are common symptoms with atrophic candidiasis.

Diagnosis of a *candida* infection is commonly based on physical exam findings. Examination of a KOH preparation of a plaque scraping may also be used; culturing is rarely necessary. Response to a trial of topical antifungal agents (clotrimazole troches are easier than liquid nystatin to use) establishes the diagnosis. If the above diagnostics do not suggest *Candida*, a biopsy of the lesion may be performed. Oral hairy leukoplakia needs to be treated only if it causes mouth pain. It can be treated with high-dose acyclovir, valacyclovir, or famciclovir.

What are the causes of painful oral ulcers in patients with HIV?

Oral ulcers are common in patients with HIV. HSV causes primary or recurrent small, smooth, painful ulcers on the lips, gums, hard palate, or buccal mucosa. They can present as solitary lesions or in clusters. Lesions often last weeks, and treatment with acyclovir can shorten the course. Patients with disseminated cytomegalovirus (CMV) infection can occasionally have a large, solitary oral lesion. Aphthous stomatitis can present as single or multiple painful ulcers on the buccal and labial mucosa and the lateral aspect of the tongue. Aphthous ulcers are often exudative or necrotic in patients with HIV, and the course is usually more prolonged than in patients without HIV. Drug therapy with zalcitabine (ddC) can also cause ulcers. In managing oral ulcers, biopsy and viral culture establishes the etiology; some suggest treating empirically for HSV. If the lesion is consistent with aphthous ulcers, treat either with topical or oral steroids or thalidomide. An oral suspension consisting of diphenhydramine, viscous lidocaine, tetracycline, and dexamethasone may offer some pain relief. Removal of the offending drug is the treatment for drug-induced ulcers.

How do you recognize and treat gingivitis and periodontal disease?

These diseases can develop either insidiously or abruptly in patients with HIV and may be severe. Gingivitis is common and can occur at any CD4 cell count. Severe pain, foul breath, bleeding gums, and loosening of teeth are common symptoms, and exam may show a bright red marginal line on the gingiva, gingival erosion, necrosis and ulceration of interdental papillae, exfoliation of enamel, and loose teeth. The cause is unclear, although aerobic and anaerobic gram-negative bacteria, spirochetes, and yeast have been implicated. Severe, ulcerating gingivitis can be caused by *Klebsiella pneumoniae*, *Enterobacter*

cloacae, and other gram-negative bacilli. Treatment includes debridement, irrigation with povidone-iodine/chlorhexidine oral solutions, and topical antiseptic agents or metronidazole.

WASTING

What are the common causes of weight loss and wasting in patients with HIV?

There can be many different psychological and physical causes of weight loss in HIV disease (see Table 8-6).

Table 8-6. Common Causes of Weight Loss in Patients with HIV

| |
|---|
| Inadequate dietary intake resulting from |
| Depression |
| Painful oral lesions |
| Esophageal lesions causing dysphagia |
| Reduced taste sensation (thrush/meds) |
| Medication side effects (eg, nausea) |
| Chronic diarrhea (malabsorption) resulting from |
| Cryptosporidia |
| Giardia |
| Hypermetabolic states |
| Infection |
| Occult malignancy (eg, B-cell lymphoma) |
| Endocrine problems |
| Hypogonadism |
| Adrenal insufficiency |
| Diabetes (PI-induced) |

How do you work up a patient with weight loss and wasting?

The workup is driven by results of the history, physical exam, and CD4 cell count; a higher CD4 count is more suggestive of causes such as endocrine disorders, malignancies, depression, or medication side effects. Serum testosterone, glucose, and thyroid tests to assess hormone status may be ordered. If malnutrition is suspected, it is important to address this promptly, since malnutrition decreases the function and number of immunity cells and leads to increased morbidity and mortality. Evaluation of GI function, calculation of caloric intake, estimation of protein and energy requirements, measurement of serum prealbumin, albumin, folate, and vitamin B12, and determination of the extent of lean body mass lost make up a comprehensive nutritional assessment. Body cell

mass can be measured using mid-arm circumference. Specific dietary deficiencies should be addressed, vitamin and mineral supplements should be prescribed, and high-calorie protein-containing foods should be recommended. In the patient with a low CD4 count (< 100 cells/mm³), OIs such as *Mycobacterium avium* complex (MAC), tuberculosis, cytomegalovirus infection, cryptosporidiosis, and *Pneumocystis carinii* pneumonia (PCP) should be ruled out, as well as lymphoma. Order a complete blood count, chemistries, blood cultures, chest x-ray, oximetry, and gastrointestinal biopsies or stool cultures as indicated. Referral to a nutritionist or registered dietician is often helpful. Also see *Health Care and HIV: Nutritional Guide for Providers and Clients* under Suggested Resources for practical assessment tools and algorithms for providers as well as patient handouts.

What are the medical treatment options for AIDS wasting?

If an underlying cause of wasting has been identified, treatment of that cause is the first step in restoring weight. One important factor may be switching to ART that does not cause gastrointestinal/anorexia symptoms preventing food intake. Any infectious process should be identified and treated. For nonspecific AIDS wasting, the mainstay of treatment is nutritional supplementation along with appetite stimulants and antiemetics. Institution of ART and prevention of OIs are important in restoring weight. Human growth hormone has been shown to rebuild lean body mass, although it is expensive and survival advantage is controversial; some recommend that it be reserved for patients who have intractable, unexplained weight loss and require short-term treatment to maintain body cell mass during an acute illness (see Table 8-7 for treatment options).

MYALGIAS

What are some common causes of myalgias in patients with HIV?

HIV can cause an inflammatory myopathy at any stage of infection. Symptoms include slowly progressive, proximal muscle weakness of the extremities with or without myalgias. Myopathy due to zidovudine (AZT) toxicity presents similarly to HIV-associated myopathy, and it may be difficult to distinguish between these two disorders. Zidovudine toxicity occurs usually after several months of therapy (most commonly after 6 or more months of continual therapy). Myopathy or rhabdomyolysis due to HMG coenzyme A reductase

inhibitors (statins) or fibrates are another important concern with HIV-infected patients. Many patients are on these drugs for treatment of hyperlipidemia caused by treatment with PIs. PIs decrease the metabolism of statins, which can increase the chance of toxicity. Moreover, many patients are on both gemfibrozil and a statin, which can interact to increase the risk of muscle toxicity. Simple myalgias are more common than rhabdomyolysis or myopathy caused by the statins.

Table 8-7. Treatment Options for Specific Causes of Weight Loss

| Cause of weight loss | Treatment options | Comments |
|----------------------|--|--|
| Anorexia | Appetite stimulants • dronabinol 2.5-5 mg/d • megestrol acetate 800 mg/d | Some studies show that weight gained is from body fat and not lean body stores. Megestrol can raise blood sugar levels, especially when used with protease inhibitors. |
| Hypogonadism | testosterone • IM 200-300 mg every 2-3 weeks • Transdermally - Patch 5 mg/day - 1% gel 5-10 g/day oxandrolone nandrolone | Liver function tests must be monitored with use of oral anabolic agents. |

How do you evaluate and manage a patient with myalgias or myopathy?

The first step is to check creatinine phosphokinase (CPK) levels. This should be done for any patient on zidovudine (AZT) or a statin who has symptoms of myalgias or muscle weakness. Periodic (every 3-6 months) monitoring of CPK levels is appropriate for patients who are on a statin/PI or statin/gemfibrozil combination. Muscle biopsy should be performed if signs and symptoms of myopathy do not remit within about a month after drug removal or if a patient has muscle enzyme elevations and is not on a drug known to cause muscle damage. Organisms may be seen on muscle biopsy, indicating an infectious myopathy. If no organisms are seen and there are signs of inflammation on biopsy, an inflammatory myopathy secondary to HIV is likely, and a trial of corticosteroids or therapy with intravenous immune globulin (IVIG) should be implemented.

DIARRHEA

What are the common causes of diarrhea in patients with HIV?

The main causes of diarrhea are related to either infections or medications. Infectious diarrhea can be caused by a number of organisms, dependent on the patient's CD4 cell count (see Table 8-8). Nelfinavir (NFV) is the antiretroviral drug most commonly associated with diarrhea. All the PIs can cause diarrhea. Didanosine (ddI) is the nucleoside most associated with diarrhea, but diarrhea is less common when the enteric coated (EC) form is used. Metformin, a drug used for treatment of lipodystrophy syndrome and diabetes, commonly causes diarrhea.

| Table 8-8. Infectious Causes of Diarrhea in Patients with HIV |
|--|
| Any CD4 cell count (acute diarrhea) |
| Viruses (especially Norwalk virus) |
| <i>Clostridium difficile</i> (previous antibiotic exposure) |
| <i>Salmonella</i> spp |
| <i>Shigella</i> spp |
| <i>Campylobacter</i> spp |
| Any CD4 cell count (chronic diarrhea) |
| <i>Clostridium difficile</i> |
| <i>Giardia lamblia</i> |
| CD4 count <300 cells/mm³ (chronic diarrhea) |
| Microsporidia |
| Cryptosporidia |
| <i>Mycobacterium avium</i> complex (CD4<100) |
| <i>Isospora belli</i> |
| Cytomegalovirus (CD4 count <100/mm ³) |
| Idiopathic |

What is the best approach to the evaluation of chronic diarrhea in the patient with HIV?

For patients who are on medication that can cause intractable diarrhea, one option is a trial of antidiarrheal medications (loperamide or atropine/phenoxylate either alone or in combination) and continuation of the previous antiretroviral regimen. If this does not work, another option is a trial off medication. If a patient is on ART, stop all medications for the 1-week evaluation

period. If there is a response, then a new agent can be substituted for the most likely causative drug, usually nelfinavir (NFV) or lopinavir plus ritonavir (LPV/r, or Kaletra). If there is no response when medications are stopped, then stool studies should be done. If the patient has a high CD4 cell count (> 300/mm³), start with *C. difficile* toxin and *Giardia* antigen. If the CD4 cell count is low (< 300/mm³), do a full workup with *C. difficile*, *Giardia* antigen, *Microsporidia*/*Cryptosporidia* assay, and modified AFB stain for cryptosporidia. If no organisms are identified, in patients with very low CD4 cell counts (< 100/mm³) obtain blood cultures for *Mycobacterium avium*, and if these are negative, pursue lower endoscopy with particular emphasis on detection of cytomegalovirus on biopsy. In patients with higher CD4 cell counts, clinical followup and trials of antimotility drugs are a reasonable approach before pursuing endoscopy.

HEADACHE

What are the important causes of headaches in HIV-infected patients?

The causes of headache vary according to CD4 cell count. Patients with a CD4 count of > 300 cells/mm³ usually have headaches with common causes such as muscle tension, migraine, or drug side effect. Sinusitis is more frequent in patients with than without HIV and may cause headaches. In patients with low CD4 counts (< 200 cells/mm³) opportunistic infections (eg, Cryptococcal meningitis, toxoplasmic encephalitis) and malignancies (eg, CNS lymphoma) are important causes to consider.

How should you work up patients with headache?

Patients with CD4 counts of < 200 cells/mm³ should have a contrast head CT scan or MRI, followed by lumbar puncture if the scan does not reveal a cause. In a study of CT scans for evaluation of headaches in HIV-positive patients *all* cases with mass lesions or white-matter lesions occurred in patients with CD4 counts of < 200 cells/mm³. Serologic tests for cryptococcal antigen and *Toxoplasma* titers are helpful in patients with CD4 counts of < 200 cells/mm³.

KEY POINTS

Antiretroviral medications are a common cause of HIV-related symptoms. Some drugs can cause life-threatening reactions and conditions, including hypersensitivity reaction, pancreatitis, lactic acidosis, and Stevens-Johnson syndrome.

The CD4 cell count and viral load are important in symptom evaluation; symptoms associated with OIs in immunocompromised patients have other causes in patients with intact immune function.

Nausea and diarrhea, very common side effects of PIs, zidovudine, and didanosine, can be managed by switching drugs or with symptomatic therapy.

Pneumococcal pneumonia, the most common bacterial pneumonia in persons with HIV, can occur early in the course of the disease, before other manifestations of immune suppression. Sinus disease is also common in persons with HIV.

Chronic fatigue requires a careful assessment to differentiate psychological from physical etiologies so that the underlying cause can be addressed.

Painful neuropathy, frequently caused by antiretroviral medications, can also result from HIV disease. Treatment may include stopping a drug or treating with tricyclic antidepressants, narcotic analgesics, or gabapentin.

Dermatologic problems common in HIV disease include pruritus, crusted scabies, herpes zoster, molluscum contagiosum, and seborrheic dermatitis.

Common oral lesions include oral candidiasis, oral hairy leukoplakia, ulcers, and gingivitis. Common causes of oral ulcers are zalcitabine, HSV, and aphthous ulcers.

Wasting may have a treatable cause, but even nonspecific AIDS wasting can be treated with nutritional supplementation, appetite stimulants and antiemetics.

Myalgia, an especially common side effect of taking a PI and a statin, may require muscle biopsy and treatment with either an antibiotic or IVIG or steroids if the condition does not improve after stopping the implicated medications.

Headaches, common with HIV disease, may be due to a CNS infection or neoplasm if the CD4 count is less than 200 cells/mm³.



SUGGESTED RESOURCES

Graham CB, Wippold FJ, Pilgram TK, Fisher EJ, Smoker WR. Screening CT of the brain determined by CD4 count in HIV-positive patients presenting with headache. *Am J Neuroradiol.* 2000; 21:451-454.

Health Care and HIV: Nutritional Guide for Providers and Clients. 2002. Rockville, MD: Health Resources and Services Administration. Available at <http://www.aidsetc.org>. Accessed 12/03.

Penzak Sr, Chuck SK, Stajich GV. Safety and efficacy of HMG-CoA reductase inhibitors for treatment of hyperlipidemia in patients with HIV infection. *Pharmacotherapy.* 2000;209:1066-1071.

CASES

1.

A 45-year-old HIV-positive man, last CD4 count 150 cells/mm³, comes to see you reporting aching in his right arm for 3 weeks. It began with only mild tenderness, but in the last week has become more painful and seems swollen. He is on ART with zidovudine (AZT), efavirenz (EFV), and nelfinavir (NFV). He is taking atorvastatin for hyperlipidemia. On physical exam, he is febrile, and his right arm is edematous and radiating heat without erythema. You obtain a CPK level which is normal.

Question: What is the most likely diagnosis?

Answer:

This patient has symptoms and signs of infectious myositis or pyomyositis, which usually develops insidiously over 2-3 weeks. In the first phase of infection, the involved muscle is tender with mild swelling. After 2-3 weeks a second phase manifests, usually with fever and edema, heat, and painful induration of the involved muscle. Erythema over the muscle is usually not seen. Laboratory values are usually notable for a lower than expected CPK but may include an elevated sedimentation rate and leukocytosis. Zidovudine-induced, statin-induced, and HIV-associated myopathy are less likely, as CPK would be elevated in these disorders, and the symptoms and signs in this patient are localized to one muscle group. Confirm the diagnosis of infectious myopathy with ultrasound or CT or MRI scanning, which will show a purulent abscess in the involved muscle. Blood cultures are not useful. If not treated, septic shock often ensues.

Question: What is the most likely cause?

Answer:

Most cases of infectious myositis are due to infection with *Staphylococcal aureus*. Other organisms reported have included *Streptococcus*, *Toxoplasma gondii*, cytomegalovirus, *Microsporidia*, *Cryptococcus neoformans*, *Mycobacterium avium intracellulare*, *Salmonella*, *Nocardia*, and gram-negative organisms.

2.

A 37-year-old man with Category 3 HIV disease (an AIDS indicator condition plus CD4 count nadir of <200 cells/mm³), last CD4 count 350 cells/mm³, comes to your office complaining of fatigue, nonspecific abdominal pain, nausea, and vomiting for the past 12 days. Review of systems is otherwise negative. He takes stavudine (d4T), zidovudine (AZT), and nelfinavir (NFV) as ART and fluoxetine for depression. On physical exam, his temperature is 37.9 degrees, respiratory rate is 25, abdomen is diffusely mildly tender to palpation, with increased tenderness in the right upper quadrant, no signs of jaundice, guaiac is negative.

Question: What is the differential diagnosis of causes related to ART?

Answer:

The differential diagnosis of ART-related etiologies in this case should include pancreatitis, based on symptoms of abdominal pain, nausea, and vomiting in a patient taking stavudine, although pancreatitis usually presents more acutely with more severe pain. Hepatitis should be considered with these symptoms in patients taking PIs. Lactic acidosis should always be suspected in a patient with these symptoms taking a nucleoside.

Question: What initial lab work should be ordered?

Answer:

Initial lab work may include CBC, basic metabolic panel, liver panel, amylase, lipase, lactate level, and coagulation studies. In the case of this patient, the lactic acid level was elevated. Further support for the diagnosis of lactic acidosis would include an increased anion gap, decreased bicarbonate, and elevated aminotransferases, lipase, amylase, CPK, and LDH.

Chapter 9:

Management of Opportunistic Diseases

Constance A. Benson, MD

OVERVIEW

PNEUMOCYSTIS JIROVECI (CARINII) PNEUMONIA (PCP)
MYCOBACTERIUM AVIUM COMPLEX (MAC)
CYTOMEGALOVIRUS INFECTION (CMV)
CANDIDA ESOPHAGITIS

CENTRAL NERVOUS SYSTEM DISEASES

MYCOBACTERIUM TUBERCULOSIS
MALIGNANCIES
KEY POINTS
SUGGESTED RESOURCES

OVERVIEW

What are the major opportunistic diseases (ODs) in patients with HIV/AIDS?

The diseases that occur as a result of HIV-related immunodeficiency include both opportunistic infections (OIs) and malignancies. The risk of developing an OI has declined dramatically with the widespread use of potent combination antiretroviral therapy (ART) (see Figure 9-1). The major OIs that occur in patients with HIV are *Pneumocystis carinii* pneumonia (the organism that causes human disease in PCP is now classified as *Pneumocystis jirovecii*, but PCP remains the conventional abbreviation in clinical use), tuberculosis, disseminated *Mycobacterium avium* complex (MAC) disease, cytomegalovirus (CMV) disease, *Candida* esophagitis, central nervous system (CNS) infections such as cryptococcal meningitis or *Toxoplasma* encephalitis, and cryptosporidiosis. While *Mycobacterium tuberculosis* is an infection that occurs in both immunocompetent and immunosuppressed patients, it remains one of the most common opportunistic co-infections in persons with HIV disease and is responsible for considerable morbidity and mortality worldwide. A host of other OIs may be seen less commonly or in patients in geographic areas where specific infections are endemic, eg, histoplasmosis in the central Midwest part of the U.S. or isosporiasis in South Florida and Puerto Rico.

See Pocket Guide Adult OI Tables 1–6

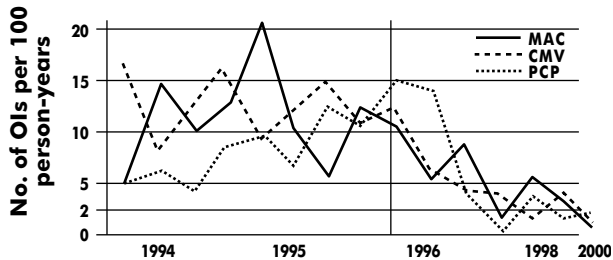
What factors are associated with higher risk of developing an OI?

OIs occur primarily in HIV-infected individuals who are not receiving either OI prophylaxis or ART (or who have not responded to it with an increase in their CD4 cell counts above the threshold that predicts risk of developing an OI). The principal risk of

Table 9-1. Risk Factors Associated with Development of Major Opportunistic Infections in HIV-Infected Individuals

| Opportunistic Infection | CD4 Count Risk Threshold (cells/mm ³) | Other Risk Factors |
|---------------------------------------|---|--|
| <i>Pneumocystis carinii</i> pneumonia | ≤200 | Prior PCP Percent CD4 cells < 14% Fever of unexplained etiology Presence of oral candidiasis |
| <i>Mycobacterium tuberculosis</i> | Any | PPD (tuberculin skin test) positive Exposure to an infectious contact |
| <i>Mycobacterium avium</i> complex | ≤50 | Prior respiratory or gastrointestinal colonization Prior OD High viral load (>10 ⁵ copies/mL) |
| Cytomegalovirus disease | ≤50 | Seropositive (IgG antibody to CMV) CMV viremia Prior OD High viral load (>10 ⁵ copies/mL) |
| Cryptococcal meningitis | ≤50-100 | Environmental exposure |
| Toxoplasmosis | ≤100-200 | Seropositive (IgG antibody to <i>T. gondii</i>) |
| <i>Candida</i> esophagitis | ≤100 | Prior <i>Candida</i> colonization High viral load (>10 ⁵ copies/mL) |
| Cryptosporidiosis | ≤100 | Environmental exposure (contaminated water, soil, animal exposure) |
| Histoplasmosis | ≤100 | Exposure (endemic areas – Midwest, Southeast U.S.) |
| Coccidioidomycosis | ≤100 | Exposure (endemic areas – Southwest U.S., Mexico) |

Figure 9-1 Decline in the Incidence of Opportunistic Infections in HIV-1-Infected Individuals Receiving Potent Combination Antiretroviral Therapy



Source: Adapted from Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853-860. Copyright 1998 by the Massachusetts Medical Society. Modified with permission (data extrapolated through 2000).

developing a specific OI is determined by the degree of immunosuppression, as measured by the CD4 cell count. The CD4 threshold of risk differs for each specific OI (see Table 9-1). It is uncommon for an OI to occur in HIV-infected individuals with CD4 cell counts above its threshold. For patients with the same CD4 cell count, those with high viral loads (plasma HIV RNA levels > 100,000 copies/mL) have a greater risk for developing an OD than those with a low viral load. Other factors that contribute to increased risk for ODs include previous exposure to or infection with a specific pathogen, prior occurrence of an OD, environmental exposure in the absence of a host response, and the use of ART.

What malignancies are associated with HIV infection?

The most common are Kaposi sarcoma (KS) and lymphomas. There is also a modest increase in the frequency of cervical cancer. In general, these 3 forms of malignancies correlate with immunosuppression, meaning the frequency increases with low CD4 cell counts, but the association is less strong than it is with the traditional AIDS-defining ODs. The rate of KS is approximately 20,000-fold higher with HIV infection compared with the general population, the frequency of non-Hodgkin lymphoma is 200- to 600-fold more frequent with HIV infection, and the rate of cervical cancer is 5-fold greater. Both lymphomas and KS are less frequent in the era of ART.

PNEUMOCYSTIS JIROVECI (CARINII) PNEUMONIA (PCP)

What are the clinical manifestations of PCP in patients with HIV infection?

PCP usually presents as an acute or subacute respiratory illness associated with fever, dyspnea, nonproductive cough, and fatigue. Physical findings on examination include tachypnea, fever, and inspiratory rales. Rarely, disseminated *Pneumocystis* occurs in HIV-infected patients with profound immunosuppression. Laboratory abnormalities associated with PCP include leukocytosis, hypoxemia, an elevated lactate dehydrogenase (LDH), and chest radiographic findings of localized or diffuse interstitial infiltrates. Occasionally, nodular or cavitory lesions may be observed. Pneumothorax in patients with advanced HIV is almost always associated with underlying *Pneumocystis* infection. The degree of hypoxemia is a measure of disease severity; severe PCP is defined as an arterial blood gas PO_2 of < 70 mm Hg with an arterial-alveolar O_2 gradient (AaO_2) of > 35 mm Hg. The diagnosis is confirmed by demonstrating the presence of *P. jiroveci* organisms in sputum or tissue samples obtained by sputum induction, bronchoscopy with bronchoalveolar lavage, or tissue biopsy. In the rare circumstance in which acute PCP presents very early with a normal chest radiograph, a gallium scan may demonstrate diffuse uptake in the lung compatible with an interstitial inflammatory process; however, this diagnostic test is nonspecific.

How should you manage PCP?

The preferred initial treatment for PCP in HIV-infected individuals is trimethoprim-sulfamethoxazole (TMP-SMX). Route of administration (oral or parenteral) is generally based on the severity of the disease. For those with severe PCP, parenteral therapy with trimethoprim 15-20 mg/kg and sulfamethoxazole 75-100 mg/kg, in 6-8 hour divided doses, is recommended. In addition, adjunctive treatment with corticosteroids, in a dose equivalent to 40 mg twice a day of prednisone for the first 5 days, followed by a tapering schedule of 40 mg/day for days 6-10, and then 20 mg/day to complete 21 days of therapy, should be initiated as soon as possible after starting treatment but preferably within the first 72 hours. For patients with mild to moderate PCP (PO_2 > 70 mmHg and AaO_2 gradient < 35 mmHg), oral treatment with 2 double-strength tablets of TMP-SMX every 8 hours is recommended. Gradual dose escalation may reduce the rate of occurrence of adverse reactions to TMP-SMX. For those unable to tolerate TMP-SMX, a number of alternative regimens are available for treatment (see Table 9-2).

| Table 9-2. Alternative Regimens for the Treatment of <i>Pneumocystis carinii</i> Pneumonia in Those Unable to Tolerate Trimethoprim and Sulfamethoxazole | |
|---|--|
| Disease Presentation | Alternative Treatment Regimens |
| Severe ($PO_2 < 70$ mm Hg; A-a O_2 gradient > 35 mm Hg) | Pentamidine 3-4 mg/kg/d IV IV Trimetrexate 45 mg/M ² /d IV + Leucovorin 0.5 mg/kg IV q6h Primaquine 15-30 mg/d (base) po + Clindamycin 600-900 mg IV q8h |
| Mild-moderate | Trimethoprim 15-20 mg/kg/d po + Dapsone 100 mg/d po q8h Primaquine 15-30 mg/d (base) p.o. + Clindamycin 300-450 mg po q6-8 hours Atovaquone suspension 750 mg po bid |

What adverse reactions occur with treatment for PCP?

Patients should be carefully monitored for adverse reactions to treatment and response to therapy. Many patients will demonstrate acute worsening of signs and symptoms and have radiographic abnormalities in the first 3-5 days of treatment. This is the rationale for adjunctive corticosteroids in those with severe PCP. Five to 7 days of treatment may be required before a clinical response is observed, defined as a reduction in fever, and improvement in hypoxemia, respiratory symptoms, and radiographic abnormalities.

Adverse reactions to treatment are common in patients with AIDS. Many patients can be treated through these with supportive care and adjunctive medications to ameliorate symptoms; however, severe adverse reactions may require substituting alternative treatment regimens. Adverse effects most often associated with TMP-SMX include skin rash (rarely, Stevens-Johnson syndrome or toxic epidermal necrolysis), fever, hepatotoxicity, leukopenia, thrombocytopenia, renal dysfunction, and hyperkalemia. Major side effects of pentamidine include pancreatitis, renal dysfunction, dysglycemia, electrolyte abnormalities, and cardiac dysrhythmias. Toxicities commonly observed with trimetrexate include bone marrow suppression (particularly in those who are not treated with leucovorin), fever, rash, and hepatitis. Dapsone may cause fever, skin rash, and methemoglobinemia with hemolysis (particularly in those with G-6-PD deficiency). Primaquine also causes methemoglobinemia and

anemia, and clindamycin toxicities include nausea, rash, hepatitis, *Clostridium difficile* toxin-associated diarrhea, and rarely toxic megacolon. Atovaquone is associated with nausea, vomiting, diarrhea, rash, fever, and hepatitis.

Is secondary prophylaxis or maintenance therapy required after treatment of the acute episode of PCP?

All patients with a CD4 count of < 200 cells/mm³ should receive primary prophylaxis to prevent PCP. All patients who have experienced an episode of PCP should receive secondary prophylaxis to prevent a recurrence of PCP. Prophylaxis should be continued for life unless immune recovery occurs with ART. Prophylaxis for PCP should be discontinued if the CD4 count increases to levels of > 200 cells/mm³ and is sustained for at least 3 months. Prophylaxis should be restarted if the CD4 count declines to < 200 cells/mm³ or if PCP recurs regardless of CD4 cell count. Table 9-3 summarizes recommended and alternative regimens for primary and secondary prevention of PCP. It should be noted that TMP-SMX and dapsone plus pyrimethamine are also adequate for prevention of toxoplasmosis in susceptible individuals; dapsone alone, atovaquone alone, and aerosolized pentamidine are not.

| Table 9-3. Recommended and Alternative Regimens for the Prevention of <i>Pneumocystis carinii</i> Pneumonia in Persons with HIV-1 Infection | |
|--|--|
| Agents | Doses |
| Preferred | |
| Trimethoprim-sulfamethoxazole | One double-strength tablet po qd One single-strength tablet po qd |
| Alternative | |
| Trimethoprim-sulfamethoxazole | One double-strength tablet po 3x/week |
| Dapsone | 100 mg po qd or 3x/week |
| Atovaquone | 1500 mg po qd |
| Dapsone + pyrimethamine + leucovorin | 200 mg + 75 mg + 25 mg po once/week |
| Aerosolized pentamidine (Respigard II) | 300 mg once/month |

MYCOBACTERIUM AVIUM COMPLEX (MAC)

What are the symptoms of MAC?

Disseminated *M. avium* complex disease is a multiorgan infection, usually occurring in patients with AIDS who have CD4 counts of < 50 cells/mm³ and principally affecting blood and lymphoreticular organs (lymph nodes, spleen, liver, bone marrow). Symptoms are nonspecific, usually consisting of high fevers, night sweats, weight loss, anorexia, and fatigue. Hepatosplenomegaly and less commonly central or peripheral lymphadenopathy are seen. Respiratory tract disease with interstitial or occasionally lobar or cavitary pulmonary infiltrates is a less common manifestation but may be seen in the context of multiorgan infection. Although there are no specific laboratory abnormalities associated with disseminated MAC, isolated elevation of alkaline phosphatase, marked anemia, and leukopenia or thrombocytopenia secondary to bone marrow infiltration may occur. The diagnosis is confirmed by the isolation of the organism from a biopsy or a sample obtained for culture from blood or involved tissue; 80%-85% of those with disseminated multiorgan disease have a positive mycobacterial blood culture. Blood cultures may require 7-10 days of incubation before growth of *M. avium* is detectable.

What is the recommended approach to treatment for disseminated MAC?

Disseminated MAC should be treated with a combination of clarithromycin 500 mg twice a day or azithromycin 500-600 mg/day plus ethambutol 15 mg/kg/day. The addition of rifabutin, 300-450 mg/day, as a third drug decreases the occurrence of relapse due to drug-resistant mycobacteria and is associated with improved survival in profoundly immunosuppressed individuals. This approach should be considered for those with very low CD4 cell counts who are not receiving or responding to ART. Treatment should be continued for life unless immune recovery occurs following ART that results in an increase in CD4 cells to levels > 100 /mm³ sustained for at least 6 months. In this setting, antimycobacterial therapy for those who have completed at least 12 months of effective treatment and have no signs or symptoms of disease may be discontinued. Therapy should be re-started if the CD4 cell count again declines to < 100 /mm³.

Primary prophylaxis to prevent disseminated *M. avium* complex disease is recommended for all HIV-infected adults and adolescents who have a CD4 count of < 50

cells/mm³. The preferred regimens are azithromycin 1200 mg once a week or clarithromycin 500 mg twice a day. Azithromycin is preferred when patients are receiving other drugs metabolized by the cytochrome P450 3A4 isoenzyme system, to avoid drug-drug interactions with clarithromycin. Rifabutin 300 mg/day is a second line alternative for prophylaxis, but is less effective than azithromycin or clarithromycin, and also must be monitored and dose-adjusted when used with other drugs metabolized by the cytochrome 3A4 isoenzyme.

CYTOMEGALOVIRUS (CMV) INFECTION

What are the major clinical syndromes associated with CMV infection in patients with HIV infection and how are they diagnosed?

Cytomegalovirus retinitis is the most common CMV-associated clinical syndrome observed in patients with AIDS. Patients with CMV retinitis involving peripheral portions of the retina may have no symptoms, or only minor visual complaints such as floaters or peripheral visual field defects. Central lesions may result in central scotomata and loss of central vision. The diagnosis is based on ophthalmologic examination demonstrating creamy white retinal exudates with hemorrhage; lesions obscure visualization of underlying vessels and other retinal structures. Retinitis is bilateral in up to 20% of patients. Disease progresses rapidly to blindness unless treated.

The second-most common clinical syndrome associated with CMV disease is gastrointestinal disease, either CMV colitis or CMV esophagitis. CMV colitis presents with fever, diarrhea, weight loss, and colon ulceration often with bleeding. Appropriate diagnosis usually requires colonoscopy and biopsy of ulcerations; tissue histopathology confirms the presence of characteristic intranuclear inclusions in mucosal cells or CMV antigens on immunohistochemical staining. CMV esophagitis presents with fever, odynophagia, and retrosternal pain. Exudative ulcers are demonstrated by esophageal endoscopic exam. Biopsy and histopathologic examination are necessary to confirm the diagnosis. Other less common CMV clinical syndromes in patients with AIDS are CMV encephalitis/encephalopathy, interstitial pneumonitis, hepatitis, and pancreatitis.

What is the recommended treatment for CMV retinitis?

CMV retinitis should be managed in cooperation with an experienced ophthalmologist. For patients with CMV retinitis that is immediately sight-threatening (central lesions approaching or involving the optic nerve or the fovea) systemic therapy with either IV ganciclovir or oral valganciclovir is the preferred initial treatment; many experts would also recommend surgical treatment with a ganciclovir intraocular implant (see Table 9-4). IV ganciclovir or oral valganciclovir is administered in an acute “induction” dose for 14-21 days, followed by a once-a-day chronic maintenance therapy dose. This approach is superior to other alternatives for preventing or delaying disease progression and provides systemic treatment to prevent other organ system involvement. If effective ART is not administered or patients remain immunosuppressed, the ocular implant should be replaced every 7-8 months. For patients with peripheral CMV retinitis that is not immediately sight-threatening, oral valganciclovir is the preferred treatment because of its ease of administration compared with other parenteral alternatives.

| Table 9-4. Treatment Options for Cytomegalovirus Disease | | |
|---|------------------------|---------------------------------|
| Drug | Induction dose | Maintenance therapy dose |
| Ganciclovir implant | N/A | Replace every 7-8 months |
| Oral valganciclovir | 900 mg bid x 14-21d | 900 mg/d |
| IV ganciclovir | 5 mg/kg bid x 14-21d | 5 mg/kg/d |
| Foscarnet | 90 mg/kg bid x 14-21d | 90 mg/kg/d |
| IV cidofovir (+ probenecid) | 5 mg/kg once/w x 2 wks | 5 mg/kg every 2 weeks |

Chronic maintenance treatment for CMV retinitis should be continued for life unless ART results in a sustained increase in CD4 counts to levels of $> 100 \text{ cells/mm}^3$ for at least 6 months. If the CD4 count again declines to $< 100 \text{ cells/mm}^3$, maintenance therapy should be reinitiated. Immune recovery vitritis is a recognized complication of acute rises in CD4 cell counts and decreases in plasma HIV RNA levels following initiation of ART. It may be associated with an acute decrease in visual acuity due to the inflammatory cells clouding the vitreous fluid. Treatment with local corticosteroids while continuing anti-CMV therapy is associated with rapid improvement in most patients.

What is the recommended treatment for CMV gastrointestinal disease?

Treatment with either oral valganciclovir or IV ganciclovir or IV foscarnet is the recommended approach to treatment of CMV esophagitis or CMV colitis. In general, clinical symptoms and signs resolve within 2-3 weeks, and the suggested duration of treatment is 21-28 days, depending on the severity of the clinical presentation. Chronic maintenance treatment is not recommended unless recurrent episodes occur.

Strategies for treatment in those with relapse or progressive disease include either re-induction followed by maintenance therapy with the same agent, or switching to an alternative agent, a combination of 2 agents, or specifically for those with CMV retinitis, systemic therapy coupled with intravitreal injection. Recurrent or progressive disease should be managed by an expert.

CANDIDA ESOPHAGITIS

What are the presenting signs and symptoms of *Candida* esophagitis and how is it diagnosed?

The most common manifestations of *Candida* esophagitis are fever, anorexia, odynophagia, and retrosternal pain. Occasionally, nausea and rarely UGI bleeding from ulceration may occur. Esophagoscopy reveals adherent whitish plaques with shallow ulcers surrounded by erythematous borders. Invasive esophageal candidiasis can occur in the absence of oral candidiasis and must be distinguished from esophagitis due to CMV, herpes simplex virus, and aphthous esophagitis, all of which may be seen in patients with HIV infection. Isolation of *Candida* species in culture from a specimen obtained from the mucosal surface or the base of an ulcer provides supportive information but is not diagnostic, as colonization of mucosal surfaces with *Candida* is common in immunosuppressed individuals, particularly those who are receiving antibacterial therapies such as TMP-SMX for prophylaxis of PCP. The diagnosis can be confirmed by a biopsy of the ulcer and demonstration of yeast forms in tissue. The finding of oral candidiasis associated with esophageal symptoms has a positive predictive value of close to 100% for *Candida* esophagitis. In patients with oral candidiasis and esophageal symptoms empiric therapy for *Candida* esophagitis should be given. If there is no clinical response after 5-7 days, upper endoscopy should be performed.

How do you treat *Candida esophagitis*?

Candida esophagitis requires systemic therapy. A number of options are available; however, the preferred treatment is fluconazole 100 mg/d for 14 days. Ketoconazole and itraconazole are effective alternatives, but drug-drug interactions with other anti-HIV therapies are common, and absorption is diminished in those with primary or drug-induced hypo- or achlorhydria. For patients unable to tolerate oral therapy, parenteral amphotericin B is effective. Chronic maintenance therapy or secondary prophylaxis is not recommended, but may be considered for patients who have frequent recurrent episodes. Chronic suppressive therapy with fluconazole has been associated with an increased risk of fluconazole (and other azole) resistant disease.

CENTRAL NERVOUS SYSTEM DISEASES

How do you distinguish cryptococcal meningitis from toxoplasmic encephalitis and CNS lymphoma in HIV-infected patients?

Patients with AIDS and a CD4 count of < 200 cells/mm³ may be at risk for developing CNS OIs such as cryptococcal meningitis or toxoplasmosis, as well as CNS lymphoma; most infections occur in those with CD4 counts of < 100 cells/mm³. Toxoplasmic encephalitis is rare in patients who are seronegative for *Toxoplasma gondii* (negative IgG antibody). CNS infection due to *T. gondii* and *Cryptococcus* spp. as well as CNS lymphoma may be relatively insidious in onset and associated with symptoms of fever, headache, and mental status changes. Focal neurological deficits and seizures are more likely to occur with toxoplasmic encephalitis and CNS lymphoma, although they sometimes occur in those with cryptococcal meningitis as well. The best diagnostic tests for a differential diagnosis of CNS disease are radiographic imaging of the CNS (with either a contrast-enhanced computerized tomographic [CT] scan or magnetic resonance imaging [MRI] scan) and lumbar puncture with cerebrospinal fluid (CSF) examination. Multiple localized enhancing lesions are common with toxoplasmic encephalitis; MRI is more sensitive than a CT scan for detecting these. CNS lymphoma is more likely to be associated with single and less commonly multiple space-occupying lesions, while cryptococcal meningitis is only rarely associated with space-occupying lesions. The CSF may demonstrate a normal to mild lymphocytic pleocytosis, normal to slightly elevated protein, and

normal to mildly decreased glucose for each, but a CSF cryptococcal antigen will be positive in 99%-100% of individuals with cryptococcal meningitis. Confirmation of the diagnosis of toxoplasmic encephalitis generally requires either demonstration of the organism in CSF by polymerase chain reaction (PCR) or culture (may not be routinely available) or a brain biopsy and demonstration of the organism in tissue. In practice, a trial of therapy is usually the first diagnostic tool for patients who have suggestive neuroimaging and positive *Toxoplasma* serology. Brain biopsy is reserved for patients who do not respond to empiric therapy. A brain biopsy is necessary to confirm the diagnosis of CNS lymphoma.

How do you treat cryptococcal meningitis?

Amphotericin B (0.7 mg/kg/d or the dose equivalent of liposomal or lipid complex amphotericin B), combined with flucytosine 100 mg/kg/day in divided doses, for the first 2 weeks, is the recommended initial treatment for cryptococcal meningitis. If a treatment response is evident this regimen is followed by fluconazole 400 mg/day for an additional 8 weeks or until CSF cultures are negative. The CSF opening pressure should always be measured when a lumbar puncture is performed, and if elevated above 200 mg H₂O, measures to reduce the pressure should be implemented. These may include serial lumbar puncture with CSF drainage sufficient to reduce the pressure by 50%, or in the case of severe increased intracranial pressure, the use of a lumbar drain or ventriculoperitoneal shunt. Secondary prophylaxis or chronic maintenance therapy with fluconazole, 200 mg/day, should be continued for life unless ART results in immune recovery. In this instance, maintenance therapy may be discontinued for those who have successfully completed a course of therapy for cryptococcal meningitis, have no residual signs or symptoms, and have a sustained increase in CD4 count to levels of > 100 - 200 cells/mm³ for at least 6 months. Maintenance therapy should be re-initiated if the CD4 count again decreases to < 100 - 200 cells/mm³.

MYCOBACTERIUM TUBERCULOSIS

Does the presentation of tuberculosis differ in HIV-infected and non-HIV-infected individuals?

Patients with HIV infection have an increased risk of infection with *Mycobacterium tuberculosis* following exposure to a person with active disease, and an

increased risk of developing active disease following an exposure. The risk of developing active disease is 30%-40% in the first year following a new exposure, and for HIV-infected patients with a positive tuberculin skin test related to prior TB exposure, the risk of developing active disease may be as high as 7%-8% per year.

For patients with a CD4 count of > 250 cells/mm³, the clinical signs and symptoms of tuberculosis are generally the same as for HIV-noninfected persons. Pulmonary tuberculosis accompanied by fever, cough, sputum production, chest pain, night sweats, weight loss, and anorexia is the principal manifestation. As immunosuppression progresses, the likelihood of extrapulmonary or disseminated (miliary) disease increases, although in most instances, pulmonary involvement is also present. Chest radiograph demonstrates lobar consolidation with cavitation, usually involving upper lobes, when reactivation tuberculosis is present. In those with primary tuberculous pneumonia, lower lobe infiltrates are more common. Hilar or mediastinal lymphadenopathy, pleural effusion, and interstitial infiltrates may be more common in patients with lower CD4 cell counts.

How do you diagnose TB in persons with HIV?

The diagnosis is the same as for non-HIV-infected persons, relying on a combination of compatible clinical signs and symptoms, radiographic findings, a positive tuberculin skin test, and a sputum sample demonstrating acid-fast bacilli (AFB). The diagnosis is confirmed by culture of the organism from sputum, blood, or other tissue. However, patients with advanced immunosuppression may have less extensive consolidation or lung cavitation, and sputum AFB smears may be positive in a lower proportion, because of the lower mycobacterial burden in the lung. Also, tuberculin skin tests are less likely to be positive because of impaired cell-mediated immune function. In immunocompromised patients, more aggressive means for making a diagnosis may be necessary, such as bronchoscopy with bronchoalveolar lavage or transbronchial biopsy to obtain samples for AFB smear and culture. Biopsy or culture of specimens obtained from extrapulmonary sites such as bone marrow and lymph nodes may be useful. All initial isolates of *M. tuberculosis* should be tested for susceptibility to antimycobacterial drugs, and susceptibility testing should guide the choice of initial treatment.

How do you treat tuberculosis in patients with HIV infection?

The recommendations for treatment of tuberculosis in patients with HIV infection depend in part on whether or not patients are on ART, and if they are, the specific antiretroviral regimens employed. All patients should receive directly observed therapy. See Adult OI Tables 2 - 7 for the recommendations for treatment of latent tuberculosis and drug-susceptible tuberculosis disease. Treatment with 4 drugs (isoniazid, rifampin or rifabutin, ethambutol, and pyrazinamide) is recommended either for the first 2 months of therapy or until results of susceptibility testing are available. If patients have drug-susceptible disease, 2 drugs, isoniazid and rifampin or rifabutin, should then be continued for at least 18 additional weeks. The continuation phase of therapy should be extended to 28 weeks (total duration of 9 months) for HIV-infected patients with advanced immunosuppression (CD4 count of < 100 cells/mm³) or who have an inadequate initial response or cavitary disease. Rifabutin should replace rifampin and doses should be appropriately adjusted for those who are receiving ART with agents likely to interact with rifamycins. The timing of initiation of ART and the most appropriate ART regimen for use in conjunction with antimycobacterial therapy remain controversial. Concurrent ART and tuberculosis treatment should be managed by an expert.

MALIGNANCIES

How does Kaposi sarcoma (KS) present?

KS is a poorly understood multicentric tumor of endothelial cells. The cause is human herpesvirus 8 (HHV-8), an infection that is more frequent in men who have sex with men. The mechanism of transmission is unclear, but the best evidence suggests transmission via saliva and semen. Many carry the virus with no consequences; it causes disease primarily in the presence of immunosuppression. The presentation is highly characteristic, with multiple purple to brown-black macules, or nodules that are usually asymptomatic and occur most frequently on the legs, face, oral cavity, or genitalia. The major complications include lymphedema (especially of the legs, face, and genitalia) and visceral involvement. Visceral involvement is common in the lung and GI tract, but is usually asymptomatic.

How do you diagnose KS?

The skin lesions are usually sufficiently characteristic to make this diagnosis clinically based on appearance, but a biopsy should be done when there is a need for confirmation. The differential diagnosis includes bacillary angiomatosis (which can be proven by biopsy with silver stain), hematoma, nevus, hemangioma, B-cell lymphoma, and pyogenic granuloma. When there is visceral involvement, the usual method used to establish the diagnosis is endoscopic examination to show typical mucosal surface lesions. With lung involvement, the x-ray is variable and may show nodules, infiltrates, effusions, and/or mediastinal/hilar nodes. Lung biopsy is often negative, but the bronchoscopic exam often shows a characteristic cherry-red bronchial nodule. With GI tract involvement, the usual screening test is stool for occult blood, and endoscopy is the usual method to make the diagnosis by showing a hemorrhagic nodule; the biopsy is often negative because of the submucosal location of the tumor.

How do you treat KS?

Many patients require no therapy except possibly makeup to cover the characteristic lesions. Topical treatment for skin involvement includes vinblastine, Panretin gel, liquid nitrogen, radiation, cryosurgery, or laser. Systemic chemotherapy is preferred when there is an extensive burden, defined as > 25 skin lesions, symptomatic visceral involvement, extensive edema, systemic (B) symptoms, or failure to respond to local treatment. The favored forms of chemotherapy are liposomal anthracyclines (Doxil or DaunoXome) or, less frequently, paclitaxel (Taxol). Immune reconstitution with ART is associated with a substantial reduction in the frequency of KS and a therapeutic improvement in those who already have these lesions. It should be noted that there is no cure for KS, and the goal of local therapy or systemic chemotherapy is to reduce tumor burden and relieve symptoms.

What lymphomas are associated with HIV infection?

The subtypes of lymphomas associated with HIV infection include B-cell large cell lymphoma, primary body effusion lymphomas, B-cell CNS lymphoma, Burkitt lymphoma, plasmablastic lymphoma, and Hodgkin disease. The most common is non-Hodgkin lymphoma.

What are the symptoms of non-Hodgkin lymphoma (NHL)?

Compared with the general population, patients with this complication have high rates of stage IV disease with systemic (B) symptoms and sparse node involvement. Common symptoms are fever of unknown origin, liver dysfunction, marrow suppression, lung disease (effusions, multinodular infiltrates, mass lesions, diffuse infiltrates, and/or hilar adenopathy), GI involvement (any level with pain and weight loss), and CNS with mass lesions.

How do you diagnose lymphomas?

Fine needle aspirates of enlarged nodes are helpful if positive, but false negatives are common. Biopsy is usually necessary.

How are lymphomas treated and what should be expected?

The usual treatment is chemotherapy with cyclophosphamide, doxorubicin, adriamycin, vincristine, and prednisone (CHOP); methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone + G-CSF (M-BACOD); or etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH). Response rates are 50% -60%, but the long-term prognosis is poor unless there is immune reconstitution with ART.

How do you diagnose and treat primary CNS lymphomas?

The typical presentation is confusion, headache, memory loss, focal neurologic changes, usually without fever and usually with a CD4 cell count of < 50/mm³. The MRI shows single or multiple lesions that are isodense or hypodense. The differential diagnosis is primarily toxoplasmosis. Factors suggesting CNS lymphoma are the characteristic MRI findings, negative *T. gondii* serology, failure to respond to empiric treatment of toxoplasmosis within 1-2 weeks, thallium single-photon emission computed tomography (thallium SPECT) scan results, and CSF positive by polymerase chain reaction (PCR) for Epstein Barr virus (EBV) DNA. The definitive diagnosis can be made by stereotactic brain biopsy. Treatment is radiation and corticosteroids, often combined with chemotherapy. The prognosis is poor without immune reconstitution.

KEY POINTS

The risk of persons with HIV developing specific ODs is related to the degree of their immunosuppression, as measured by the CD4 cell count.

All patients with a CD4 count of < 200 cells/mm³ should receive primary prophylaxis to prevent PCP. PCP usually presents as an acute or subacute respiratory illness associated with fever, dyspnea, nonproductive cough, and fatigue.

All patients with a CD4 cell count of < 50 /mm³ should receive primary prophylaxis to prevent disseminated MAC. Disseminated MAC is a multiorgan infection that usually occurs at CD4 cell counts of < 50 /mm³. Symptoms are nonspecific, usually consisting of high fever, night sweats, weight loss, anorexia, and fatigue.

CMV retinitis, the most common CMV-associated clinical syndrome, progresses rapidly to blindness unless treated. CMV gastrointestinal disease, either colitis or esophagitis, presents with fever, diarrhea, weight loss, and colon ulceration often with bleeding.

The most common manifestations of *Candida* esophagitis are fever, anorexia, odynophagia, and retrosternal pain. Treatment requires systemic therapy.

Patients with a CD4 count of < 200 cells/mm³ are at risk for developing CNS ODs such as cryptococcal meningitis or toxoplasmosis, as well as CNS lymphoma. After initial treatment, chronic maintenance therapy should be continued for life unless immune recovery occurs as a result of ART.

Patients with HIV are at increased risk of infection with *Mycobacterium tuberculosis* and of developing active tuberculosis. Immunosuppression increases the likelihood of extrapulmonary or disseminated (miliary) disease. Because tuberculin skin tests are less likely to be positive in immunocompromised patients, more aggressive means for making a diagnosis may be necessary.

All HIV-infected patients with active tuberculosis should receive directly observed therapy. Treatment of tuberculosis in persons with HIV co-infection should be managed by an expert because treatment is complex and the infection is potentially life-threatening.

The major complications of KS, a multicentric tumor of endothelial cells, include lymphedema (especially of the legs, face, and genitalia) and visceral involvement. Extent of involvement determines whether treatment is required and whether it is topical or systemic.

The most common lymphoma associated with HIV is non-Hodgkin lymphoma. Common symptoms are fever of unknown origin, liver dysfunction, marrow suppression, lung disease, GI involvement (any level with pain and weight loss), and CNS mass lesions.



SUGGESTED RESOURCES

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Chapter 10:

Abnormal Laboratory Values in HIV Disease

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COMMON ABNORMALITIES
HEMATOLOGIC COMPLICATIONS
LIVER DISEASE
RENAL DISEASE
KEY POINTS
SUGGESTED RESOURCES
REFERENCES

COMMON ABNORMALITIES

What are some common abnormalities found when screening asymptomatic patients?

Some disease processes associated with HIV can be first identified in laboratory screening tests while patients are still asymptomatic. The primary care provider plays an essential role in monitoring for laboratory abnormalities, whether these abnormalities result from diseases or from antiretroviral therapy (ART). Table 10-1 lists screening tests that assist in promptly identifying and managing medical problems in asymptomatic patients. Abnormal laboratory tests occur more frequently in HIV-infected persons because 1) HIV is a multi-system disease, 2) HIV causes immune suppression that may result in opportunistic infections and tumors that involve multiple systems, 3) the drugs used routinely in management can cause adverse reactions that affect multiple systems, and 4) patients at high risk for HIV are often at high risk for other medical conditions.

What constitutes a positive PPD in HIV disease?

Induration of 5mm or more at 48-72 hours constitutes a positive PPD test for tuberculosis in a person with HIV. A PPD should be done at baseline and repeated annually if the initial test was negative and the patient is in a high-risk category for tuberculosis. The test has a relatively high rate of false-negative results in patients with a CD4 cell count of $< 200/\text{mm}^3$. Therefore, if the initial test was done when the CD4 cell count was low, it should be repeated when the CD4 cell count increases to $> 200/\text{mm}^3$ following ART. Patients with a positive PPD test need a chest x-ray and evaluation for active disease before isoniazid (INH) prophylaxis is initiated.

What is the role of a baseline chest x-ray?

A chest x-ray is recommended for detection of latent or active tuberculosis and other lung diseases and as a baseline for patients who are at high risk for pulmonary disease, especially bacterial pneumonia, *Pneumocystis* pneumonia, and tuberculosis. The x-ray is particularly important for any patients with a positive PPD skin test.

What do you do when a patient has a positive VDRL or RPR?

The standard screening tests for syphilis in sexually active patients are the nontreponemal tests, the VDRL or RPR. Any positive screening test should be confirmed with a fluorescent treponemal antibody absorbed test (FTA-ABS). Confirmation is particularly important because for biologic false-positive tests are more common with injection drug use, pregnancy and HIV infection. With a positive test, primary, secondary, and early latent syphilis (less than 1 year) should be treated with a single injection of benzathine penicillin (2.4 million units IM) once, late latent syphilis (more than 1 year or of unknown duration) should be treated with 3 doses at 1-week intervals of benzathine penicillin (2.4 million units IM with each dose), and neurosyphilis should be treated with aqueous penicillin G, 18-24 million units/day IV for 10-14 days. Patients who are not pregnant and do not have neurosyphilis who cannot receive penicillin may be treated with doxycycline (100 mg po bid) given for 14 days for primary, secondary, and early latent syphilis and for 28 days for late latent syphilis. Because the efficacy of doxycycline is not well established, patients who received doxycycline need extra followup. With penicillin allergy and neurosyphilis or pregnancy, there should be penicillin skin testing; if negative, penicillin is given, and if positive the patient should undergo penicillin desensitization followed by penicillin treatment. A lumbar puncture is recommended for any patient with neurologic signs or

Table 10-1. Abnormalities Identified in Screening Tests

| Test | Implications of abnormal findings |
|--|---|
| CBC | Anemia – usually due to HIV or zidovudine Neutropenia – usually due to HIV or drugs, especially ganciclovir and zidovudine Thrombocytopenia – usually due to HIV |
| Alanine aminotransferase (ALT) | Usual causes of elevated levels are chronic hepatitis (HBV, HCV), alcoholic liver disease, or adverse drug reactions. |
| Creatinine | Usual causes of renal failure are common medical conditions in this population (hypertension, heroin use, diabetes, IgA nephropathy, etc), adverse reactions to drugs (including indinavir), or HIV nephropathy |
| Toxoplasma titer | Positive results in 10% of adults in US, higher in other countries. This indicates latent disease with possible activation if CD4 count < 100/mm ³ |
| VDRL or RPR | If positive, need confirmatory FTA-ABS |
| Screen for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> | Positive results indicate high-risk behavior and need for treatment |
| PPD | Induration ≥5mm indicates need for evaluation for active TB and, if negative, INH treatment |
| Chest x-ray | Ghon complex, adenopathy, or evidence of chronic lung disease |
| CD4 count | Barometer of immune function |
| Viral load | Indicates rate of progression of untreated HIV and response to HAART |
| Hepatitis panel | |
| Anti-HCV | Positive results ± confirmatory HCV RNA usually indicates chronic HCV infection |
| Anti-HBc or Anti-HBs serology | Positive results indicate prior antigenic experience with HBV |
| HBsAg | Indicates HBV; if positive >6 months indicates chronic HBV |
| Anti-HAV | Positive test indicates prior antigenic experience due to HAV infection or vaccination |

symptoms, patients with therapeutic failure (persistent clinical evidence of syphilis or a sustained 4-fold increase in titer), and all patients with latent syphilis, which includes latent syphilis of unknown duration. Some experts have recommended performing lumbar puncture for all HIV-infected persons with syphilis, regardless of the stage of syphilis. With respect to followup, the nontreponemal test should be done at 3, 6, 9, 12, and 24 months.

HEMATOLOGIC COMPLICATIONS

What are the common causes of anemia?

Anemia, which is common in HIV disease, is usually caused by 1) late-stage HIV, presumably due to viral infection of progenitor cells, 2) associated complications that infiltrate the marrow, 3) nutritional deficiency, 4) adverse drug reactions, or 5) iron deficiency. The findings and management are summarized in Table 10-2.

What causes thrombocytopenia?

Most cases are attributed to HIV infection of the multi-lineage hematopoietic progenitor cells in the marrow. This HIV-associated thrombocytopenia can occur in relatively early HIV, but is more common with late-stage disease. Although zidovudine (AZT) may cause anemia or neutropenia, early studies showed that it reverses thrombocytopenia. For patients not receiving ART, the preferred treatment for HIV-associated thrombocytopenia is to promptly initiate ART. The decision to intervene with intravenous immune globulin (IVIG) or corticosteroids is driven by signs or symptoms of active bleeding, the need to do an invasive procedure, or a lack of response to ART.

What causes neutropenia?

Neutropenia is most commonly related to drug therapy, especially with zidovudine (AZT), ganciclovir, or valganciclovir, but it can also be caused by late-stage HIV or marrow-infiltrate disease. With absolute neutrophil counts of < 500/mm³ it is important to monitor for infection and intervene with empiric antibiotics rapidly when appropriate. Address neutropenia by discontinuing the implicated agent or by providing cytokine therapy using G-CSF or GM-CSF.

| Cause | Cells | Reticulocyte count | Other tests | Treatment |
|--------------------------------|-------------------------------------|---------------------------|--|---|
| HIV disease | Normal | Low | Low erythropoietin level | ART Recombinant human erythropoietin (rHU EPO) |
| Tumors and infectious diseases | Normal | Low | Positive identification of underlying disease (eg, lymphoma, KS, MAC, TB, CMV, histoplasmosis) | Treatment of underlying disease |
| Parvovirus | Normal | 0 | Positive serology & PCR for parvovirus | IVIG |
| Nutritional deficiency | MCV > 100 (but not with AZT or d4T) | Low | Low B12/folate level | Folic acid or cobalamin |
| Iron deficiency | MCV low | Low | Blood loss, low Fe, transferrin | Treatment of cause Iron therapy |
| Drug (toxicity) | Normal | Normal | Identify offending drug (zidovudine, ganciclovir, TMP-SMX, etc.) | Stop implicated agent |
| Drug (hemolysis) | Normal | Increased | Identify offending drug (dapson, ribavirin); increased LDH, indirect bilirubin/low haptoglobin | RBC therapy Stop drug |

LIVER DISEASE

What are the common causes of abnormal liver function tests?

Abnormal screening liver function tests reflect associated conditions (hepatitis B or C viral infection as discussed below), adverse drug reactions, alcoholic hepatitis, and HIV-related complications, including Kaposi sarcoma, lymphoma, *Mycobacterium avium* complex (MAC), tuberculosis, cytomegalovirus (CMV), or histoplasmosis. Start by defining the process as cholangiopathic or hepatocellular based on results of liver function tests (LFTs).

- AIDS cholangiopathy typically presents with right upper quadrant pain, high alkaline phosphatase, characteristic duct dilatation on ultrasound, and a CD4 cell count of < 100/mm³. The usual causes are infection (microsporidia, cytomegalovirus, or cryptosporidia) or idiopathic. Most cases respond temporarily to endoscopic biliary sphincterotomy.
- Hepatocellular injury is much more common and is caused by diverse conditions, including 1) hepatitis viruses, 2) alcoholic hepatitis, 3) cirrhosis, and 4) adverse drug reactions. All antiretroviral drugs are potentially hepatotoxic, but the indications for intervention vary depending on the mechanism and severity (see Table 10-3).

When should you stop antiretroviral drugs because of hepatotoxicity?

There are 3 situations in which antiretroviral drugs should be stopped because of hepatotoxicity (see Table 10-3):

- **Hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms [DRESS])**
The hypersensitivity reaction seen with abacavir (ABC) and nevirapine (NVP) is characterized by fever, eosinophilia, rash, and GI complaints, and usually occurs during the first 6 weeks of therapy. This situation should be urgently managed, and deaths have been reported.
- **Symptomatic lactic acidosis** This is ascribed to drugs in the NRTI class, which should be stopped.
- **Increased transaminase levels** This is ascribed to the PIs and the NNRTIs nevirapine (NVP) and efavirenz (EFV). The most serious reactions have occurred with nevirapine-associated hepatotoxicity. The mechanism is unclear, and treatment interruption is often considered necessary only when clinical hepatitis occurs.

Do patients infected with HIV have increased rates of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, and does coinfection affect the natural progression of HIV?

HIV-infected patients have higher rates of chronic HBV infection after exposure to HBV. With HBV coinfection, there is a higher frequency of evidence for HBV replication (higher frequency of HBeAg and higher levels of HBV DNA) and higher rates of HBV-associated liver disease. It is not known if HBV alters the natural history of HIV, but coinfection is associated with increased frequency of hepatotoxicity with ART. The relationship with HCV is similar. HIV coinfection is relatively common, a frequency of about 30% in all HIV-infected patients and as many as 85% in those with injection drug use as the risk factor. HIV has an

Table 10-3. Antiretroviral Drugs That Cause Abnormal Liver Function

| Drugs | Frequency of abnormal liver function | Comment |
|--|--------------------------------------|--|
| NRTIs | | |
| stavudine (d4T) didanosine (ddl) zidovudine (AZT) | 8%-16% | Mitochondrial toxicity; risk highest with stavudine and didanosine together; risk with zidovudine lower than stavudine |
| lamivudine (3TC) emtricitabine (FTC) abacavir (ABC) tenofovir (TDF) | | Rare cause of mitochondrial toxicity |
| abacavir (ABC) | 4%-6% | Hypersensitivity-DRESS syndrome |
| lamivudine (3TC) emtricitabine (FTC) tenofovir (TDF) | | Withdrawal of these drugs may cause HBV exacerbation |
| NNRTIs | | |
| nevirapine (NVP) efavirenz (EFV) | 8%-16% | Mechanism not known |
| nevirapine (NVP) | Rare | Hypersensitivity – DRESS syndrome |
| PIs | | |
| All PIs | 4%-6% | Mechanism unknown |
| indinavir (IDV) atazanavir (ATV) | 10%-20% 30%-50% | Elevated indirect bilirubin; usually asymptomatic |

important effect on promoting more rapid progression of HCV, but it is not clear whether HCV adversely affects the rate of HIV progression. Many studies have shown that HCV coinfection is a poor prognostic factor in the ART era, but this may well reflect the influence of injection drug use rather than HCV-associated liver disease.

Who should you test for HBV and HCV, and what tests should you perform?

At entry into health care, all patients with HIV should be screened for antibodies to HBV and HCV, as well as HBV antigen (see Table 3-1 in Chapter 3). Knowledge of the HBV and HCV status can provide valuable information for those persons with abnormal LFTs. In addition, testing can identify patients who are seronegative for HBV who can receive HBV vaccination. Some patients with HIV have negative HBV surface antibody titers, negative HBV antigen, but positive core HBV antibody. If they have not recently acquired HBV, this serologic pattern suggests a low-level persistent immune response to HBV; these individuals probably have adequate protection to prevent reinfection, but no studies have been done to accurately evaluate their risk. Moreover, no formal recommendation exists to provide a booster HBV vaccine to those persons with negative HBV surface antibody titers but positive HBV

core antibody. Serologic testing using an enzyme immunoassay for HCV is the preferred screening test for HCV, and those with positive tests should have a confirmatory test with either the RIBA assay or a test that detects HCV RNA. Several studies have shown that some persons coinfecting with HIV and HCV, particularly those with severe advanced HIV disease, can have a negative HCV antibody test on the enzyme immunoassay, but a repeatable positive HCV RNA test. Thus, some experts would recommend doing an HCV RNA assay on a person with a negative HCV enzyme immunoassay if HCV infection is suspected (usually because of abnormal LFTs).

How should you treat HBV in persons coinfecting with HIV?

All coinfecting patients should be considered for HBV therapy. Recommendations are somewhat arbitrary, but most recommend therapy with an alanine aminotransferase (ALT) at least 2 times the upper limit of normal (ULN), evidence of active HBV replication (e antigen or HBV DNA level of > 10⁵c/mL), and preferably with histologic evidence of moderate disease activity or fibrosis. There are 2 major forms of treatment and neither is “preferred.” One form is interferon-alfa-2a or alfa-2b given subcutaneously 3 times a week or once a day for 24-48 weeks. Many authorities now

recommend pegylated interferon with subcutaneous injections once a week, although there are few published studies with this formulation for treatment of HBV. The second form of therapy is nucleosides and nucleotides with activity against HBV. This gets tricky because many of these agents are active against HIV as well, and there are variable rates of HBV resistance. Lamivudine (3TC) is highly active against HBV but is associated with high rates of HBV resistance, up to 90% at 4 years. The same applies to emtricitabine (FTC). Alternatives are adefovir dipivoxil (trade name Hepsara), which is used in a dose that is probably not active against HIV but is highly active against HBV, has good activity against lamivudine-resistant strains, and has low rates of resistance by HBV during treatment. Tenofovir (TDF) has the same attributes as adefovir but is also highly active against HIV. It should be emphasized that the rationale for treating HBV is to reduce viral replication and hepatic disease progression but that cure is rarely achieved. Other standard components of therapy in patients coinfecting with HBV are 1) advising them to avoid or limit alcohol consumption, 2) teaching them appropriate precautions to prevent transmission of both viruses, and 3) administering hepatitis A vaccine if they are susceptible.

Who should receive HBV vaccine?

All HIV-infected persons with no evidence of HBV infection should receive this vaccine, although the response rates are related to age (decreased with increasing age) and with CD4 cell counts (responses decrease with lower counts). The standard is 3 doses followed by a measurement of HBs antibody levels about 1 month after the third dose. If the level is < 10 IU/mL the 3-dose series should be repeated. If the patient does not respond to the second series, no further vaccinations are currently recommended and the patient is considered a “non-responder.”

How do you treat patients with HCV coinfection?

Patients coinfecting with HIV and HCV should be 1) advised to avoid or limit alcohol consumption, 2) counseled to use appropriate precautions to prevent transmission of both viruses, and 3) given hepatitis A and B vaccine if they are susceptible. The prevention message should emphasize that the major route of transmission is by shared needles; the risk of transmission of HCV perinatally or with sexual contact is substantially less than that for HIV or HBV.

With regard to treatment of HCV, the goal is for cure, something that cannot be achieved with HIV or, to a large extent, with HBV. All patients with HCV should be evaluated for HCV therapy. Standard indications in the absence of HIV infection are chronic HCV, detectable HCV-RNA, and a liver biopsy showing bridging or portal fibrosis. The ALT levels may be elevated, but this finding is variable and does not indicate the severity of HCV-associated liver disease and is considered nonspecific. The liver biopsy is important for HCV therapeutic decisionmaking, but it is indicated only if the patient is considered a candidate for treatment based on multiple variables including the severity and stability of HIV, other comorbidities, probability of adherence, and contraindications for interferon. The standard treatment is pegylated interferon plus ribavirin for 48 weeks, regardless of the genotype. There is limited long-term experience with this treatment in patients with HIV coinfection, but it appears that the rate of a sustained virologic response as indicated by negative HCV DNA levels at 6 months post-therapy are significantly lower compared to those who are seronegative for HIV. This particularly applies to genotype 1, which accounts for the majority of cases. It also appears that the optimal response occurs when patients have relatively high CD4 cell counts, so this treatment is often preferred for those in early stage disease and for those who have responded to ART.

What HCV therapy should you use for persons coinfecting with HIV and HCV?

Currently, there are limited published data regarding various HCV treatment regimens for persons coinfecting with HIV. Trials have generally shown relatively poor responses to interferon monotherapy. Based on rapidly accumulating data from trials that have not included HIV-infected persons, pegylated interferon (pegylated interferon-alpha-2a or pegylated interferon-alpha-2b) plus ribavirin is now the standard of care. (For treatment guidelines, refer to Suggested Resources.) In addition, several series involving persons coinfecting with HIV and HCV have suggested better sustained viral response rates with pegylated interferon plus ribavirin than with older regimens. For persons not infected with HIV, recent guidelines have recommended that those with genotypes 2 or 3 receive 24 weeks of therapy and those with genotypes 1 and 4 receive 48 weeks of therapy. The optimal duration of therapy for persons coinfecting with HIV and HCV remains unknown, but most trials have used 48 weeks, regardless of genotype.

Are there special considerations regarding adverse effects of HCV therapy in persons coinfecting with HIV?

Treatment with interferon (or pegylated interferon) and ribavirin has significant possible adverse effects, including reactions at injection sites, bone marrow suppression, thyroid dysfunction, neuropsychiatric symptoms, and birth defects. Because interferon may cause significant leukopenia, CD4 cell counts should be monitored, and patients should be warned that CD4 counts might transiently decline while they are receiving interferon. Persons coinfecting with HCV and HIV may suffer drug interactions and toxicities. Ribavirin causes anemia; because this complication occurs more frequently when ribavirin is combined with AZT, either this combination should be avoided or more frequent use of erythropoietin should be anticipated. Ribavirin may enhance intracellular didanosine (ddI) levels and augment toxicity of the drug resulting with higher rates of pancreatitis and lactic acidosis; didanosine should not be given with ribavirin.

Is liver transplantation an option for HIV-infected persons?

Liver transplantation is an option in some transplant centers that combine expertise in HIV management with the transplant service. In a study at 5 institutions of 24 HIV-infected patients survival rates were similar to rates in patients without HIV infection (Ragni et al, 2003). Nevertheless, management is complicated by problems of drug interactions between ART and the standard immunosuppressive agents, poor tolerance of ART after liver transplantation, and relatively high frequency of acute graft rejection. As in patients without HIV infection, the prognosis with liver transplantation is poorer when liver disease is caused by HCV. The recommendation at present is to give the highest priority in patients with HIV infection to those without HCV and to those receiving and tolerating ART who have achieved HIV virologic control and immune reconstitution.

RENAL DISEASE

What are the possible causes of abnormal renal function tests?

Renal function is important to monitor because abnormal renal function may require altering drug dosage regimens, and it is important to know the cause of the abnormality. In general, renal dysfunction in patients with HIV infection can be caused by adverse drug reactions, HIV-associated nephropathy, and non-HIV-related conditions. The multitude of conditions that are not necessarily complications of HIV infection or its treatment include hypertension, glomerulonephritis, and heroin use.

For the patient on ART, what drugs are most likely to cause renal disease?

Adverse drug reactions that cause renal disease are most commonly associated with aminoglycosides, amphotericin, foscarnet, and cidofovir. The antiretroviral agent that is most frequently implicated is indinavir (IDV), which may cause indinavir crystals in the collection system, resulting in nephrolithiasis. The presentation may be renal colic, or it may be asymptomatic with evidence of crystals on urinalysis. In addition, indinavir can cause a crystal-induced nephropathy. On rare occasions, tenofovir (TDF) may cause renal insufficiency.

What are the cause and implications of HIV-associated nephropathy?

HIV-associated nephropathy, which is apparently the result of HIV infection of the kidney, presents as large, echogenic kidneys on ultrasound, nephrotic-range proteinuria, and rapidly progressing renal failure. This may occur at any stage of HIV but is most common as a late complication. Pre-ART studies show benefit from treatment with ACE inhibitors and possibly with corticosteroids; more recent studies show anecdotal evidence of a sometimes dramatic response to ART, but data from controlled trials are not available. Renal biopsy is necessary to establish the diagnosis. For patients with end-stage renal disease, there is increasing interest in and experience with renal transplantation. The usual criteria are irreversible renal failure combined with HIV response to ART resulting in virologic control and a CD4 cell count of $> 200\text{mm}^3$.

KEY POINTS

Laboratory tests are frequently abnormal in HIV disease because 1) HIV is a multi-system disease, 2) HIV causes immune suppression that may result in opportunistic infections and tumors, 3) treatment has many potential adverse reactions affecting multiple systems, and 4) patients with HIV are often at high risk for other medical conditions.

Hematologic complications include anemia, neutropenia, and thrombocytopenia. The most common causes of anemia and neutropenia are either drug toxicity or the direct effect of HIV on progenitor cells; the cause of thrombocytopenia is most commonly a direct effect of HIV.

Liver disease is common because of high rates of concurrent viral hepatitis, especially HCV, and because all antiretrovirals are potentially hepatotoxic.

Abnormal renal function is usually a direct effect of HIV infection of the kidneys resulting in a rapid progression with nephrosis and end-stage renal disease; abnormal renal function from any cause is important to know about because it requires altering dose regimens for nucleosides.



SUGGESTED RESOURCES

(CONTINUED)

Management of Hepatitis C: 2002. NIH Consensus and State-of-the-Science Statements. 2002 Jun 10-12;19:1-46. Available at: <http://www.consensus.nih.gov>. Accessed 12/03.

Ogedegbe AO, Sulkowski MS. Antiretroviral-associated liver injury. *Clin Liver Dis.* 2003;7:475-499.

Orenstein R. Presenting syndromes of human immunodeficiency virus. *Mayo Clin Proc.* 2002; 77:1093-1102.

Rockstroh JK. Management of hepatitis B and C in HIV co-infected patients. *J Acquir Immune Defic Syndr.* 2003;34 Suppl 1:S59-65.

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Volberding P. Consensus statement: anemia in HIV infection--current trends, treatment options, and practice strategies. Anemia in HIV Working Group. *Clin Ther.* 2000;22:1004-1020.



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Kimmel PL, Barisoni L, Kopp JB. Pathogenesis and treatment of HIV-associated renal diseases. *Ann Intern Med.* 2003;139:214-226.

Lok ASF, McMahon BJ. AASLD Practice Guidelines *Hepatology* 2001;34:1225-1241. Available at http://www.cdc.gov/ncidod/diseases/hepatitis/b/hepatitis_b_guidelines.pdf Accessed 1/04.



WEBSITES

CDC National Center for Infectious Diseases: <http://www.cdc.gov/ncidod/diseases/hepatitis/> Accessed 2/04.

Hepatitis B Foundation: <http://www.hepb.org> Accessed 2/04.

HIV and Hepatitis: <http://www.hivandhepatitis.com> Accessed 2/04.

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Ragni MV, Belle SH, Im K, et al. Survival of human immunodeficiency virus-infected liver transplant recipients. *J Infect Dis.* 2003;188:1412-20.

Chapter 11:

Postexposure Prophylaxis

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OVERVIEW

*INTERVENTIONS FOR PEP IN HEALTH CARE SETTINGS
INTERVENTIONS FOR NONOCCUPATIONAL PEP (NPEP)
HIV PEP TREATMENT RECOMMENDATIONS
HEPATITIS PEP TREATMENT RECOMMENDATIONS*

KEY POINTS

*SUGGESTED RESOURCES
REFERENCES
CASES*

OVERVIEW

What is postexposure prophylaxis (PEP)?

Postexposure prophylaxis (PEP) prevents or aborts transmission of HIV with rapid initiation of short-term antiretroviral therapy (ART) following occupational or nonoccupational exposure. PEP should be considered in all health care personnel (HCP) and non-HCP exposed to blood or potentially infectious body fluids via percutaneous, mucous membrane, and nonintact skin exposures, injection drug use, intentional or unintentional sexual exposures, and human bites. Hepatitis B infection may be prevented following administration of immune globulin and vaccination when indicated.

PEP policies should be instituted in all health care settings. The essential elements include:

- Written protocols for documenting and managing exposures
- Assessment, counseling, and intervention immediately after any exposure
- Rapid access to medications and/or immunization, if indicated

What do we know about the effectiveness of PEP for HIV?

Retrospective case-control studies support the efficacy of PEP for occupational exposure to HIV, and 4 factors are associated with increased transmission rates: 1) deep injury, 2) visible blood on device, 3) needle placement in artery or vein, and 4) late stage HIV disease in source (this risk factor was identified prior to viral load testing, thus high viral load is likely an independent risk factor). Evidence of the effectiveness of nonoccupational PEP comes from small observational human studies,

extrapolation of data showing the interruption of maternal-infant transmission, and animal studies showing some degree of protection from genitally and intravenously acquired HIV. Even with optimal implementation, the degree of protection afforded by PEP is incomplete. Studies of PEP have demonstrated the greatest reduction in HIV transmission when antiretroviral medications are administered immediately after exposure to HIV-infected blood and body fluids. The efficacy of PEP is diminished after 36 hours and is minimal after 72 hours.

What do we know about the effectiveness of PEP for hepatitis B and C?

Hepatitis B transmission can be prevented through administration of immune globulin and hepatitis B vaccine. PEP for hepatitis C virus (HCV) has thus far proven to be ineffective.

What body fluids are infectious for HIV, HBV, HCV?

Blood is the most infectious body fluid. In the health care setting, cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids are all considered potentially infectious, although the only documented cases of occupational HIV infection have been with blood, body fluids with visible blood, or HIV viral cultures. Unless there is visible blood with the exposure, saliva, nasal discharge, tears, sweat, vomit, urine, and feces are not infectious. Semen and vaginal secretions are infectious for HIV, HBV, and HCV in the setting of nonoccupational exposure.

INTERVENTIONS FOR PEP IN HEALTH CARE SETTINGS

What types of exposures merit consideration of PEP in health care personnel (HCP)?

HCP are at increased risk from percutaneous, mucous membrane, and nonintact skin exposures to bloodborne pathogens, including hepatitis B, hepatitis C, and HIV. The risk of transmission is dependent on many factors, including the type, amount, route, and severity of exposure, the infection status of the source, and the HBV, HCV, and HIV immunity of the exposed worker (see Tables 11-1 and 11-2).

Table 11-1. High-risk Occupational Exposures

| Exposures with higher risk of transmission of bloodborne pathogens |
|---|
| Deep percutaneous injury |
| Injury with a hollow-bore blood-filled needle |
| Exposure to blood of a patient in an advanced disease stage (high viral load) |
| Exposure to a large quantity of blood or body fluids |

Table 11-2. Exposures with Low Risk of Transmission of Bloodborne Pathogens

| Exposures with low risk of transmission (PEP not recommended) |
|---|
| Blood or fluid splashes on intact skin |
| Minor scratches or abrasions without evidence of percutaneous penetration |
| Penetration by small-bore needles without visible blood |

An accurate history of the exposure is essential in determining the real risk of transmission. In studies, transmission of HIV by occupational exposure has an estimated 0.3% risk with percutaneous exposure and 0.09% with mucous membrane splash (Bell, 1997). The risk of infection for HBV (in individuals who have not been vaccinated to hepatitis B, or who were vaccine unresponsive) after percutaneous exposure is 37%-62% when the source is hepatitis B surface antigen (HbsAg) positive and hepatitis B e antigen (HBeAg) positive, and the risk of developing clinical hepatitis is 22%-31%. When the source is HbsAg positive and hepatitis B e antigen negative, the risk of HBV seroconversion is 1%-6%, and the risk of developing clinical hepatitis is 23%-37%. The risk of transmission is higher, ie 22%-31%, when the source has clinically evident hepatitis B hepatitis (Werner and Grady, 1982; CDC, 2001). Transmission of HCV through occupational exposure carries an average risk of 1.8%.

What are immediate actions and initial considerations in PEP following a possible occupational exposure?

First aid for the HCP is the first immediate action, followed by collection of information in order to assess the situation and make rapid decisions regarding appropriate treatment (see Tables 11-3, 11-4, and 11-5). Quick, expert action by the care provider is essential because the effectiveness of PEP is variable and depends on the inoculum, type of injury, potency of the PEP regimen, and speed with which treatment is started. The decision to prescribe medications, as well as medication administration, should be made within 4 hours of the exposure, and must be made within 72 hours, and preferably sooner because of studies suggesting that the efficacy of PEP is diminished after 36 hours. Even with optimal implementation, ie within the first 4 hours, the protection afforded by PEP is not 100%.

What counseling and education should you give the HCP?

The exposed HCP needs immediate counseling to assist in coping with the emotional stress of the exposure, and may require follow up care by a mental health professional. Psychological services should be available 24 hours a day, 7 days a week. A local crisis management team or an employee assistance program (EAP) may be effective ways to address this need.

The HCP should be told the relative risk of infection with HIV, HBV, and HCV following exposure, the effectiveness of PEP, and the risks and benefits of PEP. Exposed persons should be advised to return immediately if symptoms of acute HIV seroconversion occur, including fever, malaise, rash, swollen lymph nodes, fatigue or myalgias (most likely to occur 2-6 weeks after exposure).

Providers should advise exposed HCPs to prevent transmitting HIV to others, by means of the following measures, until the HCP has a negative HIV test 6 months after exposure:

- Refrain from donating blood, plasma, organs, tissue, or semen.
- Use barrier protection during sexual activity.
- If HCP is female, avoid pregnancy.
- If breast feeding, consider discontinuing, to avoid the risk of HIV transmission through breast milk.

If exposed to HBV, the HCP should follow infection control procedures that are in place at the institution.

| Table 11-3: Algorithm for Actions after Occupational Exposure to Blood or other Body Fluids Potentially Contaminated with Bloodborne Pathogens | |
|---|--|
| 1. Treat exposure site | <ul style="list-style-type: none"> Wash the exposure site immediately (not using soap). Flush mucous membranes with water. Flush eyes with water or saline solution. Do NOT apply caustic agents or antiseptics or inject disinfectants into the wound, because they may injure viable tissue and facilitate transmission. |
| 2. Gather information about the exposure | <ul style="list-style-type: none"> Date and time of exposure Details of incident Where and how exposure occurred If related to a sharp device, type and brand Details of exposure Type and amount of fluid or material |
| 3. Obtain information about the exposure source | <ul style="list-style-type: none"> Determine if possible whether source materials contained HIV, HBV, or HCV (see Table 11-4). If the source patient is HIV-positive, obtain a history of the stage of disease, viral load, history of ART, and information on ART resistance. |
| 4. Obtain information about the health care provider | <ul style="list-style-type: none"> Determine HIV status (rapid test, if possible) and, HBV vaccination and vaccine-response status (see Table 11-5). Obtain medical history, including pregnancy and breastfeeding. |
| 5. Assess the indication for PEP | <ul style="list-style-type: none"> Using this information, assess the risk of exposure to HIV and decide whether PEP is warranted in this situation. Assess the risk of exposure to HBV. |
| 6. Manage the exposure | <ul style="list-style-type: none"> Ensure appropriate and immediate access to informed counseling for all exposed HCPs, even when PEP is not recommended. If treatment for exposure to HIV is indicated, initiate medication regimen as soon as possible, and definitely within 36 hours. Do not initiate treatment after 72 hours. If treatment for exposure to hepatitis B is indicated, initiate treatment as soon as possible within 24 hours of exposure; the efficacy of HVIG after 7 days is unknown. Document counseling, postexposure management, and followup. |

| Table 11-4. Evaluation of Occupational Exposure Sources |
|---|
| Known sources |
| Test known sources for HbsAg, anti-HCV, and HIV antibody ^{a,b} : <ul style="list-style-type: none"> Direct virus assays for routine screening of source patients are not recommended. Use a rapid HIV-antibody test if available. If the source person is not infected with a bloodborne pathogen, baseline testing or further followup of the exposed person is not necessary. |
| For sources whose infection status remains unknown (eg, the source person refuses testing), consider medical diagnoses, clinical symptoms, and history of risk behaviors. |
| Do not test discarded needles for bloodborne pathogens. |
| Unknown sources |
| For unknown sources, evaluate the likelihood of exposure to a source at high risk for infection. |
| Consider likelihood of bloodborne pathogen infection among patients in the exposure setting. |

^a With attention to State regulations regarding confidentiality and informed consent.

^b If positive, confirmatory tests should be performed as appropriate including HBeAg, HIV Western blot, and HCV RNA.

Source: Centers for Disease Control and Prevention. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. *MMWR*. 2001;50(RR11):20.

| Lab tests | Comment | Frequency |
|---|---|---|
| HIV antibody test | Test HCP if source patient is HIV positive regardless of whether PEP is given | Baseline, 6 weeks, 12 weeks, 6 months (rapid test at baseline, if possible) |
| HBV | Test if source patient is HBsAg or HBeAg positive | Baseline and 4-6 months (or 1-2 months after last HBV vaccine) |
| Anti HCV | Test if source patient is HCV positive | Baseline and 4-6 months; HCV RNA at 4-6 weeks is optional |
| Liver enzymes | Test if source patient is HCV positive | Baseline and 4-6 months |
| CBC, renal function, and hepatic function | If PEP is warranted | Prior to initiating PEP and repeated in 2 weeks |

Are there special considerations for PEP in dental settings?

Although the number of exposures is relatively high in dental settings, the risk of transmission is low and no different from other HCP settings. Factors that are associated with increased risk of transmission are failure to follow PEP protocols, failure to use puncture-proof containers, treating > 20 patients per day, failure to use eye protection or masks, and male gender. For more information, see Suggested Resources.

INTERVENTIONS FOR NONOCCUPATIONAL PEP (NPEP)

What is the role of nPEP for nonoccupational exposure?

PEP for nonoccupational exposure to HIV (nPEP) is routinely being administered in cases of sexual assault in hospital emergency departments and is increasingly being made available during other cases of sexual exposure or injection drug use exposure and in non-hospital settings. This issue is particularly relevant in the care of HIV discordant couples. Research on risk of HIV transmission from a single nonoccupational exposure is relatively lacking compared with

occupational exposures (see Table 11-6). A national registry has been developed to gather the data with which to develop a CDC recommendation for HIV PEP in the nonoccupational setting. Information about this registry can be found at <http://www.hivpepregistry.org>. In general, PEP for non-HCP is modeled after PEP interventions and procedures for HCP.

| Type of exposure | Estimated risk |
|---|--|
| Needle-sharing exposure with an infected source | 0.67% |
| Receptive anal intercourse with an infected source | 0.5%-3.0% |
| Receptive vaginal intercourse with an infected source | 0.1% |
| Insertive anal intercourse with an infected source | 0.065% |
| Insertive vaginal intercourse with an infected source | 0.05% |
| Oral sex with ejaculation with an infected source | Conflicting data; however, risk is considered to be extremely low (<0.05%) |

Source: Mayer KH, Anderson DJ. Heterosexual HIV transmission. *Infect Agents Dis.* 1995;4:273-284.

What needs to be evaluated for the possible administration of PEP in the nonoccupational setting?

Factors to be considered when considering PEP for nonoccupational exposure are similar to those for occupational exposure, including 1) HIV status of potentially exposed person (a rapid test can be done in 20 minutes), 2) timing (within 72 hours, with rare exception) and frequency of exposure (recurrent exposure would require ongoing PEP and suggests need for prevention counseling as the primary intervention), 3) HIV status of source (if unknown, PEP can be initiated while this is being assessed and discontinued if HIV infection of the source cannot be confirmed), 4) transmission risk of behavior (see Table 11-6), 5) presence of other sexually transmitted diseases, particularly genital ulcer disease (which can facilitate HIV transmission). Exposures to persons who have recently seroconverted may carry a higher risk of transmission because of high HIV viremia.

What is the role of PEP for discordant couples?

Discordant couples (couples in which one person is infected and the other is not) should be routinely educated about how to protect the noninfected person. Both partners should be made aware of the possible effectiveness of PEP in cases of intended or unintended exposures and the importance of early initiation of PEP if it is to be used. Repeated, frequent exposures should signal providers to exercise caution about administration of PEP, since PEP should not be a substitute for avoidance of high-risk behavior. Any request for PEP should prompt additional counseling and psychosocial support to enhance behaviors to prevent HIV infection.

What is the role of PEP following sexual assault?

Persons who have been sexually assaulted should be considered at risk for HIV and HBV, as well as other STDs. The decision to begin PEP should not be based on the perpetrator's likelihood of infectivity or delayed pending the test results of the source (unless immediately available). Pregnancy is an important consideration when considering PEP, and emergency contraception should be considered for women who have been sexually assaulted.

A survivor of sexual assault may have had multiple exposures. When considering PEP, the most recent exposure should be considered, and PEP should be initiated if the exposure took place within 72 hours before the patient arrived at the health care facility. As with any consideration for PEP, weighing the benefits of PEP versus the possibility of medication side effects, the importance of completing the 28-day regimen and adherence issues should all be considered.

The provider should be sensitive to the psychosocial needs of the person who was sexually assaulted; the patient may not be physically or emotionally able to weigh the pros and cons about beginning PEP. Therefore, it is important to follow up within 24 hours to either emphasize the importance of adherence or to continue the discussion about initiating PEP if it is to occur within the 72-hour window.

See Suggested Resources for more information and resources in addressing issues of sexual assault.

What if the person who is exposed is a minor?

In cases involving minors, parental or guardian participation is extremely important, but parental or guardian consent for PEP may not be required. Nonetheless, in all cases, parental or guardian

participation should continue to be sought in the emergency situation and during followup. State laws and hospital policy must be considered.

HIV PEP TREATMENT RECOMMENDATIONS

If PEP is found to be appropriate, what information does the exposed person need regarding treatment?

The exposed person must understand the risks and benefits of HIV PEP, potential medication toxicities and side effects, instructions on how and when to take the medication, and the importance of adherence to the regimen, including completing the course of 28 days. Women should understand pregnancy-associated risks, including perinatal transmission and teratogenicity. Breast-feeding should be discontinued until the woman receives an HIV-negative result 6 months after exposure.

What are HIV treatment recommendations and options for PEP?

Currently recommended regimens are shown in Tables 11-7, 11-8, and 11-9; however, these recommendations may be altered if the source patient has a history of ART or known viral resistance, is pregnant, breast-feeding, has hepatic or renal disease, or is taking certain medications. If viral resistance in the source patient is known or suspected, an HIV expert should be consulted prior to initiating HIV PEP medications.

Basic HIV PEP regimens include 2 NRTIs. These regimens are relatively simple, ie 1 or 2 pills twice a day, well tolerated, and of sufficient potency to meet the needs of PEP. However, they are substantially less potent than 3-drug regimens. As noted below, some experts, including the authors, believe that only 3-drug regimens should be used for PEP, particularly in the current era of greatly simplified and somewhat better tolerated 3-drug regimens.

Three-drug regimens, comparable to highly active antiretroviral therapy (HAART) regimens used to treat HIV infection, are recommended for more severe exposures, which carry a higher risk of HIV transmission, or with exposures to sources with known HIV resistance mutations. The 3-drug regimens increase the risk of medication toxicity and may worsen adherence, all of which should be weighed when choosing an HIV PEP regimen. The majority of exposures in the past have resulted in the administration of 2 medications; 3-drug regimens

Table 11-7. Recommended HIV Postexposure Prophylaxis for Mucous Membrane Exposures and Nonintact Skin[⊖] Exposures

| Exposure Type | Infection Status of Sources | | | | |
|---------------------------|-----------------------------|-------------------------------|---|--|------------------|
| | HIV-Positive Class 1* | HIV-Positive Class 2* | Source of unknown HIV status ⁺ | Unknown source [⊖] | HIV-Negative |
| Small Volume [†] | Consider basic 2-drug PEP | Recommend basic 2-drug PEP | Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors [§] | Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely | No PEP warranted |
| Large Volume [†] | Recommend basic 2-drug PEP | Recommend expanded 3-drug PEP | Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors [§] | Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely | No PEP warranted |

[⊖] For skin exposures, follow-up is indicated only if there is evidence of compromised skin integrity (e.g., dermatitis, abrasion, or open wound).
 * HIV-Positive, Class 1 asymptomatic HIV infection or known low viral load (e.g., < 1,500 RNA copies/mL). HIV-Positive, Class 2 – symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of postexposure prophylaxis (PEP) should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.
⁺ Source of unknown HIV status (e.g., deceased source person with no samples available for HIV testing).
[⊖] Unknown source (e.g. splash from inappropriately disposed blood).
[†] Small volume (i.e., a few drops).
 ** The designation , “consider PEP,” indicates that PEP is optional and should be based on an individualized decision between the exposed person and the treating clinician.
[§] If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued.
[†] Large volume (i.e., major blood splash).

Source: Centers for Disease Control and Prevention. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. MMWR 2001;50(RR11):25.

Table 11-8: Recommended HIV Postexposure Prophylaxis for Percutaneous Injuries

| Exposure Type | Infection Status of Sources | | | | |
|--------------------------|-------------------------------|-------------------------------|---|--|------------------|
| | HIV-Positive Class 1* | HIV-Positive Class 2* | Source of unknown HIV status ⁺ | Unknown source [⊖] | HIV-Negative |
| Less Severe [†] | Recommend basic 2-drug PEP | Recommend expanded 3-drug PEP | Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors [§] | Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely | No PEP warranted |
| More Severe [†] | Recommend expanded 3-drug PEP | Recommend expanded 3-drug PEP | Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors [§] | Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely | No PEP warranted |

* HIV-Positive, Class 1 asymptomatic HIV infection or known low viral load (e.g., < 1,500 RNA copies/mL). HIV-Positive, Class 2 – symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of postexposure prophylaxis (PEP) should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.
⁺ Source of unknown HIV status (e.g., deceased source person with no samples available for HIV testing).
[⊖] Unknown source (e.g. a needle from a sharps disposal container).
[†] Less severe (e.g., solid needle and superficial injury).
 ** The designation , “consider PEP,” indicates that PEP is optional and should be based on an individualized decision between the exposed person and the treating clinician.
[§] If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued.
[†] More severe (e.g. large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient’s artery or vein).

Source: Centers for Disease Control and Prevention. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. MMWR 2001;50(RR11):24.

Table 11-9. Treatment Options for 2- and 3-drug PEP

| Table 11-9. Treatment Options for 2- and 3-drug PEP | |
|---|--|
| | Treatment Options |
| Basic 2-drug PEP | zidovudine (AZT) 300 mg bid + lamivudine (3TC) 150 mg bid (may be taken as Combivir bid) |
| | stavudine (d4T) 40 mg bid + 3TC 150 mg bid |
| | stavudine (d4T) 40 mg bid + didanosine (ddI) 400 mg qd on an empty stomach (No longer recommended because of increased toxicity unless a suitable alternative is not available.) |
| 3-drug PEP | One of the above NRTI* combinations plus a third drug, usually a PI**, an NTRTI#, or an NNRTI,*** to be determined in consultation with an HIV expert. |
| | nevirapine (NVP) (No longer recommended for PEP due to the potential for severe liver toxicity.) |

* NRTI: nucleoside or nucleoside reverse transcriptase inhibitor

** PI: protease inhibitor

NTRTI: nucleotide reverse transcriptase inhibitor, i.e., tenofovir (TDF)

*** NNRTI: non-nucleoside reverse transcriptase inhibitors, i.e., efavirenz (EFV)

should be chosen with the advice of an HIV expert. In accordance with the same principles that are used in treating HIV-positive persons; some experts believe that 3-drug PEP regimens should be the mainstay of PEP and that 2-drug regimens should be used only during extenuating circumstances such as an inability to tolerate a protease inhibitor (PI). For example, the New York State PEP Guidelines now recommend zidovudine and lamivudine (Combivir) plus tenofovir (two pills in the morning and one pill in the evening) as the standard PEP intervention. (<http://www.hivguidelines.org>)

Although the current data on PEP for nonoccupational HIV exposures are scant, treatment recommendations for occupational PEP can be generalized to nonoccupationally exposed persons. As in the case of PEP in HCP, nonjudgmental counseling directed towards the reduction of future exposures is an important part of PEP in nonHCP.

What are the side effects of HIV PEP?

Side effects of HIV PEP regimens are common and occur in 30%-50% of patients. Severe side effects occur in 5%-30% of patients and often require discontinuation. Common side effects include gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain; rash; fatigue; headache and dizziness; cytopenia; neuropathy; hepatitis; and many others. In reported series to date, over half of HCP in PEP programs fail to complete their 28-day regimens because of side effects. Regularly scheduled

followup either in person or by phone has been shown to greatly improve adherence. Refer to other chapters for more detail on symptom management and metabolic complications with ART.

What medication toxicities should be monitored?

Regular laboratory evaluation for medication toxicity and seroconversion should be performed (see Table 11-5). A complete blood count and renal and hepatic function tests should be done before initiating PEP and repeated in 2 weeks. Continued monitoring is recommended for abnormal lab test results, and medication changes should be considered if abnormalities are severe. Specific monitoring parameters vary with the regimen; for example, glucose levels should be monitored if a PI is used. If the PI is indinavir (IDV) a urinalysis should also be checked to monitor for crystalluria and hematuria. Tenofovir (TDF) is well tolerated, but should be used with caution and careful monitoring in patients with compromised renal function (Refer to Drug Information Tables in the Pocket Guide for medication side effects.)

Two regimens deserve special consideration. Hepatotoxicity, Stevens-Johnson syndrome, and fatal hepatic necrosis have occurred in HCP treated with nevirapine (NVP) as part of their PEP regimen, and therefore its use is not recommended, given the variety of other options. Pregnant women treated with stavudine (d4T) and didanosine (ddI) were found to be at increased risk for fatal and non-fatal lactic acidosis, and therefore this combination is not recommended in the treatment of pregnant women. In addition, recent clinical trial data showed a higher rate of adverse effects with the combination of stavudine and didanosine in adults, and their use in combination is not recommended unless other alternatives are not available.

What are the treatment recommendations when the source patient is known to have specific HIV resistance mutations?

Resistance to HIV medications is an important consideration in the treatment of HIV-positive persons, and known resistance in the source patient should be a consideration when choosing an appropriate HIV PEP regimen. In addition, because of reported increases in resistance mutations in recently acquired HIV infection in several cities in the United States, resistance is increasingly a concern in untreated patients, and thus for PEP in exposures to unknown sources. HIV PEP failures attributed to exposure to resistant virus have been reported in the literature.

Unfortunately, resistance test results are often unavailable at the time of the consideration of PEP, and PEP should not be unduly delayed while this information is sought. A thorough drug, adherence, and HIV history from the source patient and consultation with an HIV expert is needed to make the optimal treatment recommendation.

When should expert consultation be sought?

Expert consultation is potentially valuable in many circumstances with PEP. As above, expert consultation is indicated in the setting of known or suspected drug resistance in the source in order to select drugs to which the patient's virus is likely to be susceptible. Other situations include:

- Delayed report of exposure, since the interval after which there is no benefit from PEP is undefined, in order to determine if PEP is still indicated
- Unknown status of the source, since the decision regarding the use of PEP should be individualized, based on the estimated likelihood of risk to the HCP, considering the severity of the exposure and the epidemiologic likelihood of HIV exposure
- Known or suspected pregnancy in the exposed person, in which case specific treatment recommendations may require modification
- Possible toxicity of the initial PEP regimen, in which case modification of the regimen and/or treatment of the adverse side effect may be considered

HEPATITIS PEP TREATMENT RECOMMENDATIONS

What are the treatment recommendations and options for possible hepatitis B exposure?

HBIG and immunization against HBV following exposure are the most effective methods to prevent HBV transmission (see Table 11-10). PEP for HBV with multiple doses of HBIG has been shown to be 75%-95% effective. Pregnant women can safely receive both the HBV vaccination and HBIG. When considering PEP for HBV exposures, both the source patient's HbsAg status and the exposed person's vaccination status and antibody response should be considered. Both HBIG and the hepatitis B vaccine should be administered within 24 hours of exposure. Anti-HBs should be drawn 1-2 months after completion of the third vaccine, but it is unreliable if the exposed person has received HBIG within the past 3-4 months.

Table 11-10. Recommended Postexposure Prophylaxis for Exposure to Hepatitis B Virus

| Vaccination and antibody response status of exposed workers* | Treatment | | |
|--|--|------------------------------------|---|
| | Source HBsAg positive ⁺ | Source HBsAg ⁺ negative | Source of unknown or not available for testing |
| Unvaccinated | HBIG [§] x 1 and initiate HR vaccine series [†] | | |
| Previously vaccinated | | | |
| Known responder** | No treatment | No treatment | No Treatment |
| Known nonresponder [⊖] | HBIG x 1 and initiate revaccination or HVIG x 2 [†] | No treatment | If know high risk source, treat as if sources were HBsAg positive |
| Antibody response unknown | Test exposed person for anti-HBs ^{††} 1. If adequate**, no treatment is necessary 2. If inadequate [⊖] , administer HBIG x 1 and vaccine booster | No treatment | Test exposed person for anti-HBs 1. If adequate [†] , no treatment is necessary 2. If inadequate [†] , administer vaccine booster and recheck titer in 1-2 months |

* Persons who have previously been infected with HBV are immune to reinfection and do not require postexposure prophylaxis.

⁺ Hepatitis B surface antigen.

[§] Hepatitis B immune globulin; dose is 0.06 mL/kg intramuscularly.

[†] Hepatitis B vaccine.

** A responder is a person with adequate levels of serum antibody to HBsAg (ie, anti-HBs ≥ 10mIU/mL).

⊖ A nonresponder is a person with inadequate response to vaccination (ie, serum anti-HBs < 10mIU/mL).

[†] The option of giving one dose of HBIG and reinitiating the vaccine series is preferred for nonresponders who have not completed a second 3-dose vaccine series. For persons who have previously completed a second vaccine series but failed to respond, two doses of HBIG are preferred.

^{††} Antibody to HBsAg.

Source: Centers for Disease Control and Prevention. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. *MMWR* 2001;50(RR11):22.

What are the treatment recommendations and options for possible hepatitis C exposure?

There are no recommended prophylactic treatments after exposure to HCV blood or body fluids. Current data do not support treatment during acute HCV infection at this time; referral of an individual with recently acquired HCV to a specialist in HCV care is appropriate.

Following exposure, testing should be performed on the source for anti-HCV. If positive, the exposed person should be tested for anti-HCV and alanine

aminotransferase (ALT) initially and in 4-6 months. HCV-RNA and ALT at 4-6 weeks are optional. All anti-HCV results should be confirmed by recombinant immunoblot assay; if positive an HCV RNA should be drawn. Drawing an HCV RNA at 4-6 weeks may be done for earlier diagnosis, but the person should be counseled that false-positives do occur. Current research supports early diagnosis of HCV as basis for the most effective management after exposure are known. Exposed persons should be counseled to refrain from donating blood, plasma, organs, tissue, or semen. Although the transmission risk by sexual activity is low, it is reasonable to recommend a barrier method until the results of testing 6 months after exposure are known. There are currently no recommendations to make any changes in breast-feeding, pregnancy, or professional activities. Mental health counseling should be offered as needed.

KEY POINTS

The goals of PEP are to prevent or abort the transmission of HIV and hepatitis B virus (HBV) and to enable early diagnosis of hepatitis C virus (HCV).

All exposed persons need followup within 24-48 hours depending on the pathogen.

HIV PEP, if determined to be appropriate, should be provided preferably immediately, and definitely within 36 hours of exposure. PEP is NOT recommended for minor exposures. If the provider is inexperienced in using HIV medications or managing PEP patients, an HIV specialist should be consulted before initiating treatment.

The risk of transmission of HBV is far greater than of HIV or HCV. All HCPs should be vaccinated against HBV. HBIG is highly effective in preventing transmission of HBV.

There is currently no recommended PEP medication for HCV. If possible, the source should be tested for antiHCV, and if positive, the exposed person should be monitored.

PEP should be available in all health care settings. PEP protocols should be developed, regularly updated, and included in regular employee training programs.

PEP for nonoccupational exposure (nPEP) is modeled after PEP for occupational exposures. nPEP is routinely administered in cases of sexual assault in emergency departments, and is increasingly being made available for other cases of sexual exposure or injection drug use exposure in non-hospital settings.



SUGGESTED RESOURCES

Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. Available at <http://aidsinfo.nih.gov/guidelines/>.

PEP Steps—a pocket summary of the 2001 PEP Guidelines. Mountain Plains AIDS Education and Training Center. Available at <http://www.uchsc.edu/mpaetc/hivresources.htm> or by telephone at 303-315-2516.

Practice recommendations for health-care facilities implementing the U.S. Public Health Service guidelines for management of occupational exposures to bloodborne pathogens. *MMWR* 2001;50(RR-11):43-44. Available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a2.htm>.

Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States. Available at <http://www.hivatis.org>.



WEBSITES

Food and Drug Administration: <http://www.fda.gov>. Accessed 1/04.

Hepatitis information: <http://www.cdc.gov/hepatitis>. Accessed 1/04.

HIV PEP registry, for nonoccupational exposures: <http://www.hivpepregistry.org>. Accessed 1/04.

National Rape, Abuse, & Incest National Network: <http://www.rainn.org/>. Accessed 1/04.

Needlestick website, a web-based expert system to help providers manage and document occupational exposures to blood and bodily fluids: <http://www.needlestick.mednet.ucla.edu>. Accessed 1/04.

New York State Department of Health AIDS Institute, PEP guidelines: <http://www.hivguidelines.org>. Accessed 1/04.

STD/HIV Prevention Training Centers (PTCs): <http://depts.washington.edu/nnptc> Accessed 10/03.

Contact State and local health departments for additional information.



TELEPHONE

National Rape Crisis Hotline: 1-800-658-HOPE.

National Clinicians' Post-Exposure Prophylaxis Hotline (PEpline), expert consultation for providers on occupational exposures to bloodborne pathogens: 1-888-HIV-4911 (1-888-448-4911) or <http://www.ucsf.edu/hivcntr/resources/pep>. Accessed 1/04.

Warmline: National HIV telephone consultation service: 1-800-933-3413

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New York State Department of Health AIDS Institute. *HIV PEP Guidelines.* Available at <http://www.hivguidelines.org> Accessed 1/04.

Mayer KH, Anderson DJ. Heterosexual HIV transmission. *Infect Agents Dis.* 1995;4:273-284.

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CASES

1.

An employee states that she has just punctured herself with a needle after drawing a patient's blood. The patient has already left the clinic and no one knows anything about his medical history. The employee completed the HBV vaccination series and is hepatitis B surface antibody (HBsAb) positive. During the investigation the HIV prevalence in this setting was found to be low.

Question: What is the risk of HIV transmission?

Answer:

The risk of HIV transmission after a puncture wound with a hollow-bore needle is 0.3%. It is important to remember that the risk of infection is higher when there is a large-volume exposure, a deep percutaneous injury, or an injury with a hollow-bore, blood-filled needle, or if the source has advanced HIV disease or has a high level of HIV viremia. The current CDC recommendations advise against HIV PEP when the source is unknown and in settings where the HIV prevalence is low.

Question: What counseling and followup should be recommended?

Answer:

Because of the low prevalence of HIV in this setting, the employee should be advised against taking HIV medications. Also, because she is HBsAb positive she is not a candidate for HBV PEP. The HCP should be advised to refrain from donating blood, plasma, organs, or tissue, to use barrier methods during sexual activities, and to refrain from sharing any injection or other drug use equipment. She should also be counseled about universal precautions and administration should take steps to reduce the risk of future accidental needle sticks. She should be educated about the symptoms of acute HIV and advised to return immediately if those symptoms occur. Mental health counseling should also be offered.

A baseline HIV antibody and anti-HCV should be drawn. HIV antibody should be repeated at 6 weeks, 3 months and 6 months after exposure. A 12-month followup is recommended if the source is found to be coinfecting with HIV and HCV, or if the exposed becomes infected with HCV following exposure. Anti-HCV and ALT should be repeated within 4-6 months and if positive should be confirmed with supplemental tests.

2.

A patient known to be HIV negative 6 months ago comes to the clinic stating that last night he was the receptive partner of unprotected sexual intercourse with his HIV-positive partner when the condom broke. His partner has been HIV-positive for 5 years, currently has an undetectable viral load, and is taking Combivir (zidovudine + lamivudine) and efavirenz (EFV). He has never had a resistance test.

Question: Should the patient take HIV PEP medications?

Answer:

Although the current recommendations for nonoccupational exposures were released in 1998 and at that time found that PEP for nonoccupational HIV exposure was still unproven, current data support treating. Receptive anal intercourse with an HIV-positive partner carries with it a risk of transmission of 0.5%-3.0%. Your patient's risk is likely lower because of his partner's low level of viremia. PEP in nonoccupational settings is modeled after PEP for HCPs. In this case, the patient had a large exposure from a known HIV-positive source with an undetectable viral load.

Following the model for PEP for HCPs, the patient should be treated ASAP, ie within 4 to 72 hours but not more than 72 hours after exposure and receive 2 medications, although some experts would recommend using 3 medications. It would be reasonable to place the patient on the same combination as his partner because his partner has exhibited good adherence and good virologic control. Treatment should continue for 28 days.

The patient should be counseled about medication side effects and the importance of adherence and followup. Common side effects should be anticipated and pre-empted with counseling and, in some cases, treatment. Changing medications and/or modifying the dosage regimen may increase the likelihood of completion of the HIV PEP regimen. And finally, the patient should be educated about the symptoms of acute HIV infection and advised to return immediately if those symptoms occur.

Question: What lab specimens should be drawn?

Answer:

A baseline HIV Ab should be drawn and repeated at 6 weeks, 3 months, 6 months and 12 months after exposure, as well as an HBsAg, HBsAb, and HCV Ab. If he were unvaccinated against HAV or HBV then vaccination should be initiated immediately. Laboratory monitoring for drug toxicity should be performed at baseline and then 2 weeks after initiating therapy. The medical record of the patient's partner should immediately be reviewed, and treatment for HBV, HCV, or other sexually transmitted diseases should occur, if any of these are found. Expert consultation should be sought if needed.

Chapter 12:

Family Planning and Pregnancy

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CARE OF HIV-POSITIVE WOMEN OF CHILDBEARING AGE

PREVENTING MOTHER-TO-CHILD TRANSMISSION (MTCT)

PERINATAL CARE FOR PREGNANT WOMEN WITH HIV

KEY POINTS

SUGGESTED RESOURCES

REFERENCES

CARE OF HIV-POSITIVE WOMEN OF CHILDBEARING AGE

When should you provide pregnancy counseling to women living with HIV who are of childbearing age?

More than half the pregnancies in the United States are unplanned. For women living with HIV, education and counseling about pregnancy and HIV should be done early in the course of HIV care, not delayed until the woman is pregnant, so that she can make informed decisions about contraception and pregnancy. Many women with HIV mistakenly assume they cannot get pregnant and need to be educated before it is too late.

What counseling interventions should be included in primary care?

All women of childbearing age should receive the benefit of preconceptional counseling as part of routine primary medical care (ACOG, 1995). Women who have HIV should also be counseled about:

- The impact of HIV on the course and outcome of pregnancy
- The impact of pregnancy on HIV progression
- Appropriate contraception to prevent unintended pregnancies
- Perinatal transmission risks, including strategies to reduce the risk of perinatal transmission
- Permanency planning (guardian issues for children)

What primary care interventions are appropriate for women with HIV who want to become pregnant?

Certain measures can help facilitate a successful pregnancy if a woman with HIV wants to become pregnant:

- Institute routine preconceptional care such as genetic screening, screening for STDs, PAP smear, and initiation of folic acid supplementation.
- For women already on antiretroviral therapy (ART) or who have indications for therapy, ensure that medications are not contraindicated in pregnancy (efavirenz [EFV] is contraindicated) and optimize therapy to reduce viral load and reduce side effects.
- Vaccinate as indicated.
- Optimize maternal nutritional status.
- Screen for psychological and substance abuse disorders and treat.
- Refer for perinatal consultation as needed.

Are there options for HIV-positive individuals who are considering reproduction?

There are centers in the United States and in Europe that provide “sperm washing” to decrease the possibility of HIV transmission to the woman during planned conception. However, this method has not been well studied and, as a practical matter, is not available to most HIV discordant couples (Kim et al, 1999). Discordant couples who choose to become pregnant need to be educated about the risk of HIV transmission. To reduce the risk if the man is HIV-positive, his viral load should be as low as possible,

intercurrent STDs should be treated, and attempts to conceive should be well timed around ovulation to avoid unnecessary exposures during periods of decreased fertility. The American College of Obstetricians and Gynecologists has recently endorsed the use of reproductive technology in HIV-infected patients (ACOG, 2004). Which patients should be offered assisted reproduction and what the optimal methods are of decreasing heterosexual and perinatal HIV transmission must be determined.

When should pregnancy testing be done?

Since most pregnancies are unplanned, the diagnosis of pregnancy frequently occurs late in the first trimester, when organogenesis is nearly complete. In order to make the diagnosis earlier, pregnancy tests should be done when sexually active women have:

- Late or missed menses (unless she is using Norplant or Depo-Provera)
- Irregular bleeding (unless she is using Norplant or Depo-Provera)
- New onset of irregular bleeding after prolonged amenorrhea with Norplant/Depo-Provera
- New onset of pelvic pain
- Enlarged uterus or adnexal mass on exam

In addition, women with the potential of becoming pregnant should be tested before starting potentially teratogenic therapies such as efavirenz (EFV), which is the only antiretroviral drug that is contraindicated in pregnancy. Patients should be alerted to potential teratogenic effects on the fetus, and suitable contraception should be prescribed.

What contraceptive methods are recommended for women with HIV who do not want to become pregnant?

Condoms are the most common contraceptive method used by women living with HIV. Condoms, consistently used, have the added advantage of providing protection against STDs, including potential reinfection with HIV. This benefit should be emphasized when contraceptive advice is given to an HIV-positive or at-risk woman even if she is not seeking or does not need contraception but is sexually active.

Hormonal methods of contraception are also frequently used (delivered orally, by injection, or by skin patch). However, there are many important drug interactions between hormonal contraceptives and drugs used to treat HIV infection and HIV-related complications (see next question).

What are the most common drug interactions between oral contraceptives and drugs used in HIV disease?

Oral contraceptives significantly interact with amprenavir/fosamprenavir (APV/FAPV), efavirenz (EFV), lopinavir (LPV), nelfinavir (NFV), nevirapine (NVP), and ritonavir (RTV); an additional method of contraception, such as condoms, is recommended. Similarly, other drugs commonly used by HIV-infected patients, including tetracycline, rifampin, oral anticoagulants, beta-blockers, and antidepressants interact with oral contraceptives, and an additional means of contraception is advisable. Indinavir and atazanavir do not appear to have an interaction.

What contraceptive methods are not highly recommended for women with HIV who do not want to become pregnant?

Spermicides: Generally, a spermicide should be used along with a barrier method to increase its effectiveness. However, in some studies nonoxynol-9 (the active ingredient in spermicidal contraceptives) has been found to cause vaginal irritation and epithelial inflammation when used as the sole contraceptive method and on a regular and frequent basis. This may increase the risk of HIV transmission.

Intrauterine Device: The intrauterine device (IUD) is not recommended for HIV-infected women. The IUD is associated with pelvic inflammatory disease and is also associated with increased menstrual flow. Some studies even suggest that this device is linked to increased susceptibility to HIV transmission.

PREVENTING MOTHER-TO-CHILD TRANSMISSION (MTCT)

Which are the current recommendations for HIV testing of pregnant women?

Since prevention of vertical transmission (from mother to child) of HIV is so effective, identification of HIV infection in all women who are pregnant is imperative. Therefore:

- HIV testing should be a routine part of prenatal care for all women. The “opt out” method, in which HIV testing is included in the routine bloodwork and pregnant women have to refuse the test, results in higher test rates and should be used.

- Testing should be performed as early as possible in pregnancy to allow for timely interventions and decisions.
- HIV-negative women who are at high risk of acquiring HIV should be retested in the third trimester of pregnancy (ideally before 36 weeks). Women are at high risk if they have a history of STDs, exchange sex for money or drugs, have multiple sex partners during pregnancy, use illicit drugs, have HIV-positive or high-risk sex partners, and/or show signs and symptoms of seroconversion.
- Women whose HIV status is unknown and/or who present late in pregnancy or already in labor should be assessed promptly for HIV infection, using rapid HIV testing, to allow for timely prophylactic treatment. Standard confirmatory tests should be done after delivery for women with positive rapid test results.
- CDC recommends timely, routine screening of an infant if the mother has not been tested during pregnancy or delivery (CDC, 2003).

How should HIV testing be done?

HIV testing should be voluntary, and providers should carefully document informed consent. Providers should offer pre- and post-test counseling that includes information on modes of transmission of the virus, risk factors that might be present even if a woman has only one sex partner, and effective interventions to reduce the risk of perinatal transmission of HIV. There should be a discussion of services available for the provision of medical care, and the woman should be reassured that care for her and her infant will not be denied if she declines the test. Laws and regulations on HIV screening of pregnant women and their infants vary by State. Therefore, providers should be familiar with the State regulations and policies that apply to them (CDC, 2001).

When does transmission from mother to infant occur and what are risk factors for transmission?

Vertical transmission can occur during the perinatal period and infancy, that is, before or close to the time of birth or during breastfeeding. Risk factors associated with vertical transmission include (CDC, 2001):

- Advanced disease in the mother
- High plasma viral load
- Maternal injection drug use during pregnancy
- Preterm delivery
- HCV coinfection
- Failure to follow the recommended regimen of zidovudine prophylaxis
- Breast-feeding

- Delivery more than 4 hours after rupture of membranes
- Concurrent STDs
- Chorioamnionitis
- Certain obstetrical procedures

How common is vertical transmission of HIV with and without ART?

In the absence of antiretrovirals, the perinatal transmission rate of HIV infection is approximately 25%. There is a direct correlation between maternal viral load as measured by plasma HIV-1 RNA and probability of perinatal transmission. A large study showed that the rate of perinatal transmission among women with viral load > 100,000 c/mL was 40.6%, with 50,001 to 100,000 c/mL it was 30.9%, with 10,001 to 50,000 c/mL it was 21.3%, with 1,000 to 10,000 c/mL it was 16.6%; and with < 1,000 c/mL it was 0% (Garcia et al, 1999).

Treatment with zidovudine (AZT) alone can reduce transmission to close to 8%. Multi-agent antiretroviral therapy can reduce the transmission rate even further (see Table 12-1).

Table 12-1. Antiretroviral Treatment and Perinatal Transmission

| Treatment category | Number treated | HIV transmission rate (95% confidence interval) |
|-------------------------|----------------|---|
| Untreated | 396 | 20.0% (16.1, 23.9) |
| AZT monotherapy | 710 | 10.4% (8.2, 12.6) |
| Dual therapy, non-HAART | 186 | 3.8% (1.1, 6.5) |
| HAART | 250 | 1.2% (0, 2.5) |

Source: Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr.* 2002;29:484-494.

Do pregnant women with very low or undetectable viral loads need ART?

Yes. All pregnant women should receive ART. Analysis of the first study of the effectiveness of ART in reducing perinatal transmission (ACTG 076 study) showed that zidovudine (AZT) significantly reduced perinatal transmission even when the baseline viral load was < 1,000 c/mL (Ioannidis et al, 2001). This study provides the rationale for zidovudine monotherapy in untreated pregnant women with a baseline viral load of < 1,000 c/mL.

What pharmacologic interventions are recommended to reduce the risk of MTCT?

ART should be offered to **all** HIV-infected pregnant women, and zidovudine chemoprophylaxis should be incorporated into the antiretroviral regimen to prevent perinatal transmission because safety and efficacy data are greatest for zidovudine (PHS, 2002) (see Pocket Guide Pregnancy Table 1). Zidovudine prophylaxis is associated with significant reduction in perinatal transmission that is independent of viral load (Sperling, 1996; Shapiro et al, 1999) and of zidovudine resistance (Eastman et al, 1998).

Are there additional interventions to reduce the risk of MTCT and improve maternal/fetal health?

When the woman is HIV positive there are interventions that can reduce the risk of MTCT.

- Pregnant women with HIV should be counseled to refrain from cigarette smoking, injection and illicit drug use, and unprotected sexual intercourse with multiple sex partners.
- STDs in pregnancy should be treated since they are associated with a higher risk of vertical transmission.

Can cesarean section reduce the risk of MTCT?

Elective cesarean section reduces the risk of perinatal transmission and should be offered at 38 weeks to pregnant women when the viral load is likely to be > 1,000 c/mL at delivery (Dominguez, 2003). ACOG in a joint statement with the American Academy of Pediatrics (AAP) recommended offering HIV-positive pregnant women scheduled cesarean section at 38 weeks gestation (AAP, ACOG, 1999; CDC, 2001), rather than waiting until 39 weeks. *There is no evidence of benefit of C-section after onset of labor, after rupture of membranes, or in women with viral loads of < 1000 c/mL.*

What interventions should occur during a scheduled cesarean section?

When a scheduled cesarean section is planned, intravenous zidovudine should start 3 hours before surgery according to standard dosing (see Pocket Guide Pregnancy Table 5). Since infectious morbidity is potentially increased, the obstetrician should consider antibiotic prophylaxis. Other antiretrovirals should not be interrupted at the time of delivery regardless of route of delivery.

What should you advise mothers about breastfeeding?

The risk of HIV transmission with breastfeeding is approximately 16%. Avoidance of breastfeeding is recommended in the United States and other industrialized countries since replacement feeding is safe and accessible. In resource-poor countries where risks of replacement feeding include malnutrition and infections other than HIV, the World Health Organization recommends exclusive breastfeeding during the first 3 months of life since **exclusive** breastfeeding carries a lower risk of HIV transmission than mixed feeding. To minimize the risk of HIV transmission in these settings, breastfeeding by HIV-positive women should be discontinued as soon as feasible, taking into consideration local circumstances and the risks of replacement feeding (WHO, 2001).

What testing should neonates of HIV-positive mothers receive?

When neonates are born to HIV-positive mothers, serial testing for HIV should be done within the first few days of life, at age 1 month, and again at 4-6 months or later (AAP, ACOG, 2002). Early identification of HIV in neonates is crucial for adequate management. Since maternal antibody may be present, HIV antibody testing is not useful until the baby is 18 months old. Using either HIV-DNA PCR or HIV culture, however, pediatricians can usually determine the HIV status of infants by the age of 4 months.

PERINATAL CARE FOR PREGNANT WOMEN WITH HIV

What medical and counseling interventions are appropriate for pregnant women with HIV?

Initial evaluation of an HIV-positive pregnant woman should include an assessment of her HIV disease status. Besides the standard components of prenatal care indicated for all pregnant women, the provider should obtain CD4 cell counts and viral loads, and resistance tests should be performed. Viral loads and CD4 counts should be repeated every 3 months.

The goals of ART during pregnancy are to:

- optimize the health of the woman
- protect the fetus from HIV
- provide regimens that are neither toxic for the woman nor teratogenic for the fetus.

Clinicians should discuss short- and long-term benefits and risks for both the woman and the fetus before initiating or modifying ART. Options should be presented in a non-coercive way, and the final decision always lies with the patient. A long-term plan should be developed, and the importance of adherence to ART should be stressed.

What antiretroviral regimens are recommended for pregnant women with HIV?

The use of the 3-part zidovudine (AZT) chemoprophylaxis regimen, alone or in combination with other antiretroviral agents, should **always** be offered and discussed with all infected pregnant women to reduce the risk of perinatal HIV transmission (see Pocket Guide Pregnancy Table 3). Any pregnant woman with HIV should be offered a treatment regimen that adheres to the currently recommended treatment for HIV-infected adults, which generally consists of 2 reverse transcriptase inhibitors into which zidovudine is incorporated, plus a protease inhibitor (see Pocket Guide Pregnancy Table 4). Efavirenz (EFV) is contraindicated in the first trimester because it has been associated with birth defects in a monkey model. Referral to providers who are experienced in the care of pregnant HIV-infected women is recommended.

Are there special considerations when a woman already on ART becomes pregnant?

When an HIV-infected woman receiving ART is found to be pregnant after the first trimester she should be counseled to continue therapy. Zidovudine should be a component of the antenatal ART regimen after the first trimester whenever possible, although this may not always be feasible. A woman receiving ART whose pregnancy is recognized during the first trimester should be counseled regarding the benefits and potential risks of continuing ART during this period of organogenesis. As discussed above, efavirenz (EFV) is contraindicated in the first trimester. Also, dapson, a folic acid antagonist, has been reported to increase the risk for neural tube defects. Maternal absorption and metabolism of protease inhibitors (PIs) change during pregnancy, and there are specific recommendations for dose adjustments of nelfinavir (NFV) (<http://www.aidsinfo.nih.gov>).

What are some of the problems that may occur when antiretroviral agents are prescribed during pregnancy?

Hyperglycemia and diabetic ketoacidosis have been reported with PI use during pregnancy. Therefore, pregnant women using PIs should be carefully instructed to watch for symptoms of hyperglycemia, and blood glucose levels should be closely monitored.

Lactic acidosis is more common in the last trimester of pregnancy, and hepatic enzymes and serum electrolytes should be monitored frequently during the last trimester in pregnant women receiving nucleoside analogues. The combination of stavudine (d4T) and didanosine (ddI) in HIV-positive pregnant women is not recommended as it has been associated with maternal mortality from severe lactic acidosis.

Hyperemesis gravidarum is a common complication of pregnancy. If a woman needs to discontinue ART because of pregnancy-related hyperemesis, she should not restart medications until sufficient time has elapsed to ensure that the drugs will be tolerated; all drugs should be stopped at once and reintroduced simultaneously to reduce the potential for emergence of resistance.

What medical and counseling interventions are appropriate for postpartum followup of women with HIV?

Comprehensive care and support services, including primary, obstetric, pediatric, and HIV specialty care, family planning services, mental health and substance abuse treatment, and coordination of care through case management for the woman, her children, and other family members are important for women with HIV and their families. Maternal medical services during the postpartum period must be coordinated between the obstetric care provider and the HIV specialist. When treatment is required for the woman's HIV infection, continuity of ART must be assured.

What followup should be done for the infants of mothers with HIV?

Infants of HIV-positive women on ART should be followed for potential side effects of antiretroviral medications even if the infants are HIV-negative; followup should continue into adulthood because of the theoretical concerns regarding potential carcinogenicity of the nucleoside analogue antiretroviral drugs. Infected children should be followed to determine their need for prophylactic treatment or ART, as well as to assess possible delays in growth and development.

Where should prenatal exposure cases be reported?

Cases of prenatal exposure should be reported to the Antiretroviral Pregnancy Registry. This registry collects anonymous observational data. The Registry can be contacted at:

Antiretroviral Pregnancy Registry
115 N. Third St., Suite 28401
Wilmington, NC 28401
Tel: 800-258-4263
FAX: 800-800-1052

KEY POINTS

All HIV-positive women of childbearing age should receive information about the impact of HIV on the course and outcome of pregnancy, the impact of pregnancy on HIV progression, and appropriate contraception to prevent unintended pregnancy.

To assure early identification of pregnancy in women with HIV who are sexually active, pregnancy tests should be done whenever they have late or missed menses or other signs of possible pregnancy. Women with the potential of becoming pregnant should be tested before starting potentially teratogenic therapies such as efavirenz (EFV). Patients should be alerted on potential teratogenic effects on the fetus, and suitable contraception should be prescribed.

Contraceptive methods recommended for women with HIV include condoms, which also protect against STDs and prevent HIV transmission to their partners, and hormonal methods. The drug interactions between oral contraceptives and many drugs used in HIV disease make an additional means of contraception advisable in many cases. Spermicides and intrauterine devices are not recommended for use by HIV-infected women.

HIV testing should be a routine part of prenatal care for all women. HIV testing should be voluntary using the “opt out” method (the HIV test is part of routine bloodwork and the woman may opt to refuse the test). Pre- and post-test HIV counseling should be provided.

All pregnant women infected with HIV should receive antiretroviral therapy. Zidovudine monotherapy can be provided to untreated pregnant women with a baseline viral load of < 1,000 c/mL, but a 3-part ART regimen including zidovudine should always be offered and discussed. Pregnant women should be offered the currently recommended treatment regimens for HIV-infected adults, except that efavirenz (EFV) is contraindicated in the first trimester.

Medical problems associated with ART during pregnancy include hyperglycemia and diabetic ketoacidosis, lactic acidosis, and hyperemesis gravidarum.



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Chapter 13:

Management of Substance Abuse

Henry Francis, MD

ASSESSMENT OF SUBSTANCE ABUSE PROBLEMS
TREATMENT OF SUBSTANCE ABUSE PROBLEMS
MEDICAL AND PAIN MANAGEMENT ISSUES
HIV/AIDS ISSUES
KEY POINTS
SUGGESTED RESOURCES
REFERENCES

ASSESSMENT OF SUBSTANCE ABUSE PROBLEMS

What is the definition of a substance abuser?

A substance abuser is an individual who repeatedly uses an addictive substance or performs a certain behavior even with the knowledge of its negative health consequences. A person is drug dependent or addicted if he or she uses drugs repeatedly despite the social, interpersonal, or other problems associated with their use and has a physical or psychological tolerance to the drug and experiences withdrawal symptoms after the effects of the drug wear off. Long-term drug abuse can interfere with normal brain activity and metabolism and can become a chronic, relapsing condition characterized by compulsive drug craving and drug seeking. There are other kinds of addiction that may not involve the use of substances, such as gambling, sex, and eating-related disorders, all of which involve a range of dysfunctional behaviors with undesirable social, medical, and economic consequences (see Table 13-1).

| Table 13-1: Range of Substances and Behaviors That Can Be Abused | |
|---|---|
| Addictive substances | Behaviors |
| <ul style="list-style-type: none"> • Marijuana • Cocaine • Heroin • Amphetamines, other stimulants • Tranquilizers • Hallucinogens • Steroids and recreational drugs | <ul style="list-style-type: none"> • Eating disorders: anorexia, bulimia, bingeing • Sex disorders: compulsive sexual activity • Gambling • Internet addictions: compulsive use of the internet |

How should primary care providers address substance use problems in their patients?

The first task is to consciously look for behavioral and physical signs of maladaptive drug use and to use a simple screening tool such as the CAGE examination (described below) to detect it. Common indicators of drug abuse are frequent absence from work or school, recurrent injuries, motor vehicle accidents, depression, anxiety, labile hypertension, sleep problems, sexual dysfunction, or abdominal symptoms. Physical signs of drug abuse such as tremor, liver disorders, and physical changes such as nasal irritation caused by cocaine are well known to health care providers.

The second task is to tell the patient his or her diagnosis of drug abuse or dependence. Providers are often concerned about upsetting a patient with a stigmatizing diagnosis. Giving a concise, objective description of clinical findings without making judgments is important. Common pitfalls for providers to avoid during this discussion are listed as the DEATH Glossary (Table 13-2).

The third task before sending a patient to treatment is to try a brief intervention in the office. It has clearly been shown that brief interventions given in community centers, hospitals, and ambulatory clinics decrease the morbidity and mortality associated with drug abuse (see Suggested Resources). For physicians who have received training on buprenorphine treatment for opiate addicts, there is the added opportunity to treat opiate drug users in the private practice setting without referring the individuals to drug use centers (see section on Treatment of Substance Abuse below).

| Table 13-2: The DEATH Glossary | |
|---|--|
| Common Pitfalls for Providers to Avoid when Diagnosing Drug Abuse Problems | |
| D Drinking or Drug-use | Details are not relevant; talking with a person on drugs is not useful. The simple issue here is talking to the patient when he or she is sober, ie, has not taken a drug before the visit. |
| E Etiology | Do not spend much time on how drug use started but focus on getting the person to treatment. |
| A Argument | Avoid arguing at all costs. No meaningful conversation will occur in an argument. |
| T Threats | Guilt and shame do not promote recovery from chemical dependency. Threats or evoking guilt will not promote successful therapy. |
| H Hedging | Hedging hurts your credibility. Being ambivalent about giving the diagnosis will not help the patient. If the patient disagrees with you, unequivocally agreeing to disagree is a valid starting point for getting to successful recovery. |

Diagnosing drug or alcohol dependence or addiction is not an easy task. Many people who are addicted to alcohol or drugs attempt to conceal or deny that they have an addiction. In addition, diagnostic tests for drug dependence and addiction lack specificity and sensitivity. Although blood and urine tests are usually quite reliable at detecting recent drug use, individuals can be adept at avoiding being tested or at manipulating test results. See Table 13-3 for the duration of time substances are detectable in urine.

| Table 13-3: Duration of Time Drugs Are Detectable in Urine | |
|---|----------------------------|
| Substance | Duration |
| Alcohol | 48 hours |
| Amphetamines | 12 hours |
| Barbiturates | 10-30 days |
| Valium | 4-5 days |
| Cocaine | 24-72 hours |
| Heroin | 24 hours |
| Marijuana | 3-30 days (in heavy users) |
| Methaqualone | 4-24 days |
| Phencyclidine (PCP) | 3-10 days |
| Methadone | 3 days |
| Sex, food, gambling | Not applicable |

13

Why is substance abuse such a big issue in HIV care?

Injection drug use is estimated to be responsible for 25% of HIV transmission in the United States and is directly or indirectly responsible for 57% of HIV transmission to women. Less well appreciated is the fact that drug-using behaviors may be a significant HIV transmission risk factor for many men who do not inject drugs. In a recent study of men who have sex with men (MSM), up to 16% may have drug use as a risk factor for acquiring HIV (Chesney, 2003). The high degree of association between injection and noninjection drug use underscores the importance of primary care providers' being able to diagnose drug using behaviors.

Are there tools to help providers assess patients for drug and alcohol use?

Experts in addiction medicine use a combination of behavioral and clinical testing to diagnose drug abuse. There are 9 commonly used drug-use screening tests: Addiction Severity Index (ASI), Alcohol Dependence Scale, Alcohol Use Disorders Identification Test (AUDIT), CAGE (see below), Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar), Drinker Inventory of Consequences (DrInC), Michigan Alcohol Screening Test (MAST and SMAST), Problem Oriented Screening Instrument for Teenagers (POSIT), and Self-Administered Alcoholism Screening Test (SAAST) (American Society of Addiction Medicine, 1998). Six of them are specifically designed to detect alcohol use.

Which screening tests are most useful in primary care practice?

The CAGE test is a non-threatening quick screening test for detecting drug use in adults (see Table 13-4) and the POSIT test useful for screening adolescents aged 12-19. The questions below are designed to assess key substance-using behaviors. The letters in CAGE correspond to important emotions or behaviors indicative of drug use.

| Table 13-4: The CAGE Screening Test | |
|-------------------------------------|---|
| C | 1. Have you felt that you ought to C ut down on your drinking or drug use? |
| A | 2. Have people A nnoyed you by criticizing your drinking or drug use? |
| G | 3. Have you ever felt bad or G uilty about your drinking or drug use? |
| E | 4. Have you ever had a drink or used drugs first thing in the morning (E ye opener) to steady your nerves, to get rid of a hangover, or to get the day started? |

The Problem Oriented Screening Instrument for Teenagers (POSIT) examination is a 139 item yes/no questionnaire for assessing adolescent risk factors in substance abuse, physical health, mental health, family and peer relationships, educational and vocational status, social skills, leisure and recreation, aggressive behavior, and delinquency. A nonexperienced provider can conduct the test in 20 to 25 minutes. The questionnaire is available free in English and Spanish from the National Clearinghouse for Alcohol and Drug Information by mail at P.O. Box 2345, Rockville, MD 20847-2345 or by telephone at 1-800-729-6686.

What would provide a more in-depth assessment of drug and alcohol use?

Two detailed evaluations of drug and alcohol use are the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and Addiction Severity Index (ASI) for alcohol or drug use. The DSM-IV defines the diagnostic criteria for substance dependence as a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by 3 or more of the following, occurring at any time in the same 12-month period:

1. Presence of drug withdrawal symptoms
2. Escalation of drug doses

3. Persistent inability to reduce or control drug use
4. Increased time spent obtaining drugs
5. Personal and business activities reduced by drug use
6. Development of drug tolerance
7. Knowing drug use's negative health and personal effects, yet continuing to use drugs

TREATMENT OF SUBSTANCE ABUSE PROBLEMS

What should you do before referring a person for treatment?

The decision to refer a person for drug abuse treatment should come after the provider has detected a substance use problem, conducted initial evaluations to determine the degree of drug use and physical harm done by the drug use, and provided brief interventions to stop drug abuse. After the diagnosis and brief interventions (if appropriate), the provider should refer the patient to a drug treatment system or an addiction physician.

What role does the primary care provider's attitude play in successful drug abuse treatment?

Drug abuse treatment is successful if the provider addresses his or her own biases about addiction, understands the factors contributing to addiction, provides appropriate pharmacologic and behavioral care, and recognizes that drug addiction is a chronic disease problem. Many drug abuse treatment failures are associated with hostile or unsupportive providers whose behaviors are based on the assumption that drug use is voluntary. Since successful drug abuse therapy depends on adherence to treatment regimens, any factors that facilitate adherence will foster successful treatment outcomes. The patient's perception that the primary care provider is nonjudgmental and supportive is an essential factor in successful therapy.

How can the primary care provider enhance the success of drug abuse treatment?

The primary care provider must prevent or treat exogenous factors that negatively affect successful drug abuse therapy. We now recognize significant environmental (social), genetic, biologic, and behavioral factors that facilitate drug addiction:

Environmental factors Common factors are family or sibling drug use, poverty, poor education, and homelessness. Patient referral to social services and family referral into drug treatment will facilitate the patient's therapy.

Genetic factors Ten percent of drug users have multifactorial genetic predispositions to drug use. Many patients have significant severe drug use problems requiring care from addiction specialists as soon as possible.

Biologic factors Many patients have preexisting mental health problems such as depression and attention deficit and hyperactivity disorder (ADHD) which, if recognized and treated, may prevent or modulate drug use.

Behavioral risk factors For adolescents, peer pressure is a common cause of drug use. Early education by parents and the primary care physician about drug use are very important for preventing drug use by adolescents.

What is the role of drug detoxification in drug abuse treatment?

Drug detoxification is the transitional therapy between identifying drug abuse and beginning a comprehensive program to treat it. The objective of drug detoxification is to facilitate a safe drug withdrawal process in supportive surroundings. Detoxification is not a treatment or cure for drug addiction; it is an intervention to get a person to the stage of comprehensive drug abuse therapy. Two common medical interventions to modulate symptoms are benzodiazepines in alcohol withdrawal and clonidine in opiate withdrawal.

What are the components of a comprehensive drug abuse treatment plan?

Effective drug abuse treatment encompasses a combination of behavioral and pharmacologic therapies to treat the individual's particular substance abuse problems and needs. Drug use medication is only one element of successful, comprehensive drug treatment, which includes addressing the individual's medical, psychological, social, vocational, and legal problems (see Table 13-5). Behavioral drug abuse prevention and treatment programs are provided in residential settings and in prisons. These programs may provide

medications to treat drug abuse, medical treatment for coexisting illnesses, and /or behavioral interventions using a number of personal, family, and community interventions. The most important community interventions are the 12-step or self help programs such as Narcotics Anonymous, Cocaine Anonymous, and Alcoholics Anonymous.

What should you do after the patient has completed a drug treatment program?

The primary care provider's task in assuring successful drug addiction treatment is to treat drug abuse as a chronic disease. Drug abuse treatment is effective if provided correctly and consistently. Approximately 50% of alcoholics, 60% of opiate addicts, 55% of cocaine addicts, and 30% of nicotine (cigarette) addicts are successfully treated. Note the success rate is generally lower for the legal addictive drugs, which may be because of ready access to those substances. For the illicit drug addictions, success occurs only if the drug abuse therapy is given on a continual basis for the lifetime of the patient. Drug use studies have clearly shown that drug abusers will relapse as any patient would who has a chronic disease. In direct comparisons, drug-addicted patients are actually less likely to relapse into addiction and are more adherent to their medication than persons with diabetes mellitus or hypertension.

| Table 13-5: Components of Drug Abuse Treatment | |
|---|---|
| Personal needs | Treatment needs |
| <ul style="list-style-type: none"> • Family services • Housing and transport • Financial services • Legal services • AIDS/HIV services • Educational service • Medical service • Vocational service • Child care service | <ul style="list-style-type: none"> • Behavioral therapy • Clinical and case management • Intake and processing • Treatment plans • Pharmacotherapy • Continuing care • Substance use monitoring • Self help/peer support groups |

How do you use maintenance medications in treating drug abuse?

Maintenance treatment medications, important adjuncts to comprehensive drug abuse and dependence treatment, are used in the same way the nicotine patch is used for cigarette smokers. The medications help stabilize the drug user by reducing drug craving and thereby reducing high-risk behaviors associated with acquiring illicit drugs to attain the drug-induced high. Medication is used most effectively by patients who have good social support and higher education levels and are highly motivated to get off illicit drugs.

What are the common medications used in drug abuse treatment?

Use of medications to treat illicit drug use is limited because most of the approved medications are for opiate addiction and alcohol abuse. Effective opiate addiction medications are divided into 2 classes: opiate agonists and opiate antagonists. Opiate agonists are used to substitute for the opiate without causing the euphoria associated with drug abuse. The opiate agonists include methadone, L-alpha-acetyl-methadol (LAAM), and buprenorphine, which has recently been approved for medical use in the United States (Johnson, 2000). The other class is the opiate antagonists, the most important of which is naltrexone. Buprenorphine, actually a partial agonist-antagonist, may be used by physicians who undergo an 8-hour training course on how to use the medication. This medication has the highest potential for providing care in the private practice setting. Details for obtaining buprenorphine training and certification are available at the Office of Substance Abuse and Mental Health Administrations website, www.samhsa.gov, in the addiction treatment section under office-based therapies.

How do you detect, manage, and prevent relapse?

After the patient has been treated and is off drugs, the responsibility of the primary care physician does not end. The most common complication after patients have stopped using drugs is relapse. Four points to remember: 1) relapse should be expected to occur in most users; 2) on average 3-4 episodes may occur before complete abstinence; 3) relapse is not a treatment failure; it is a time to intensify treatment; and 4) the primary care provider is critical in preventing episodes of relapse. The most critical issues for the primary care provider to keep track of in the detection and prevention of relapses are to:

- Provide close followup.
- Do not make medical care dependent on drug abstinence.

- Recognize missed appointments as a sign of relapse and need for followup.
- Encourage and monitor the drug treatment/sobriety program of the patient.
- Treat comorbid psychiatric conditions aggressively.
- Identify drug use trigger points with the patient and discuss how to avoid them.
- Develop a plan to identify and manage relapse early.
- Make every effort to keep communication open and nonjudgmental.

MEDICAL AND PAIN MANAGEMENT ISSUES

What exactly do drugs do to the brain?

Researchers continue to explore the variety of functional and structural changes that occur in the brain during drug use. Drug dependencies have been linked to disturbances in the dopaminergic pathways of the mesolimbic reward system, which lies deep in the brain. This system interconnects the ventral tegumentum to the nucleus accumbens with other connections to the limbic system and orbitofrontal cortex (Leshner, 1997). Disturbances in these areas are responsible for the behavioral changes and drug craving that characterize the drug-addicted person. Brain imaging studies have suggested that the changes in the brain are chronic, even after the person stops consuming drugs and may cause the relapses of most drug users.

What are the common medical problems of patients who inject drugs?

Patients who inject drugs often have comorbid clinical conditions, which are listed below with specific recommendations.

Mental health problems Treat early. Depression is the most common problem.

Hepatitis C Screen all drug users for hepatitis C and B and treat when indicated. Consult a specialist in HIV/AIDS and hepatitis C for coinfecting patients. Screen for depression before initiating therapy for hepatitis C. Treating hepatitis is important for preventing hepatotoxicity associated with ART.

Sexually transmitted diseases Screen regularly and provide safe sex education. Like other people, drug users often do not stop having sex even if they are infected with multiple diseases.

Tuberculosis Past tuberculosis exposure is common in injection drug users (as many as 30% are PPD positive); they should be screened for TB.

Skin and soft tissue infections Cellulitis and skin abscesses are very common in injection drug users. The practice of “skin popping” markedly increases the risk of abscess formation.

Noninfectious health problems Treat accordingly. Drug users and alcoholics have multiple health problems that should be treated aggressively. The fewer medical problems patients have, the more likely they are to adhere to the treatment plan. Common problems to be aware of:

- Drug interactions (between medications and between medications and illicit drugs)
- Diabetes mellitus and hypertension
- Social environment (housing, child care)
- Pain management

How do you manage pain in opiate-addicted patients?

It is incorrect to assume that individuals addicted to opiates or any other kind of drug should receive less pain medication because they are addicted. They should receive pain therapy based on the diagnosed cause of the pain just like nonaddicted patients. The therapeutic approach differs according to whether the pain is acute or chronic.

How should you treat acute pain in a person diagnosed as a drug abuser?

Appropriate actions to take for drug-abusing patients in acute pain related to a recent diagnosable injury involve managing the pain:

1. Determine the source of the pain.
2. Provide pain medication that relieves the symptoms. Opiates may be used if they are what will stop the pain.
3. Give the medication in regularly scheduled doses. This prevents undesirable drug-seeking behaviors resulting from treatment on an as-needed (PRN) basis.
4. If pain is persistent or the cause is unclear, check for underlying psychiatric problems or an undetected source of pain.
5. If opiates are used, taper the doses slowly to avoid drug withdrawal.

How should you treat chronic pain in a person diagnosed as a drug abuser?

If the pain is chronic, the treatment strategies shift to not only finding the source of the pain, but also to using the entire spectrum of pain-relieving strategies with or without nonopiate pain medication (see Table 13-6). One exception is a patient with cancer-associated pain, for whom any effective medication (potentially addictive or not) is appropriate.

| Table 13-6: Treatments for Chronic Pain in Known Drug Abusers |
|--|
| Medications used for pain control |
| Nonsteroidal anti-inflammatory drugs (eg, 30 mg ketorolactromethamine, which is equivalent to 6-10 mg morphine) Tricyclics Anticonvulsants Muscle relaxants Topical agents Opiates |
| Physical interventions for pain control |
| <i>Thermal:</i> heat and cold are both effective and underutilized <i>Peripheral counterstimulation:</i> transcutaneous electrical nerve stimulation (TENS) and vibration <i>Manual therapies:</i> massage and chiropractic and osteopathic manipulation <i>Active movement:</i> stretching and active exercise <i>Orthotics:</i> splints and other supportive devices |

HIV/AIDS ISSUES

Can HIV transmission be prevented in active substance abusers?

A comprehensive HIV prevention strategy in a primary care practice includes interventions to provide drug treatment, to take care of mental health problems, and to prevent HIV transmission during drug use and sexual activity. The primary care provider should routinely screen for drug abuse and treat or refer for treatment as quickly as possible. This is particularly important for adolescents who are at high risk for HIV, hepatitis B and C, and other infections. One study has shown that once adolescents start injecting drugs, over 90% will become infected with hepatitis C within 18 months. The provider should also counsel patients who are actively using drugs not to share needles with others and to take advantage of programs that distribute clean needles. Programs use the needle distribution strategy as a first step to engage individuals who can then be encouraged to accept medical and drug abuse treatment services.

When is an active substance abuser ready for HIV treatment?

The most important clinical decision for successful treatment of drug-abusing patients with HIV is deciding when they are ready -- both substance abuse treatment and antiretroviral therapy (ART). Patients fall into 3 categories: those who do not want treatment, those who are ambivalent, and those who want treatment. For patients who do not want treatment, the provider should continue to be available with information on HIV and drug abuse treatment until they are ready to consider treatment. For those who are ambivalent about treatment, time is well spent during several clinical visits discussing the health issues of AIDS and drug abuse until they are ready for treatment. For patients who are ready for treatment the next step is to assess what factors will affect their adherence (see Chapter 7: Adherence to HIV Therapies). History of injection drug use, race, gender, age, socioeconomic status, level of education, and occupation are poor predictors of medication adherence. Accurate predictors of adherence are:

- The patient's health beliefs
- Ease of access to health care providers
- Familiarity with the treatment setting
- Existence of a social support system

- Perceived support from clinical staff members
- Simplicity of medication regimens

Interaction with providers and ambiance of the treatment setting account for almost half of the support factors needed to encourage drug users to adhere to treatment regimens. This pattern is true for active drug users, with the possible exception of persons addicted to crack cocaine.

Difficult economic and social situations, including unemployment and unstable housing, may make adherence to clinical treatment plans for both drug addiction and HIV even more difficult to follow. For these reasons some drug abuse treatment centers provide residential treatment to minimize outside influences on drug use. Also, methadone clinics provide an ideal opportunity for rehabilitated substance users to receive adherence support for ART through directly observed therapy (DOT) at the clinic.

What immunizations should drug abusers with HIV receive?

Because of the higher risk of tetanus in injection drug users, tetanus boosters should be given when due. Pneumococcal and influenza vaccines are recommended for all patients with HIV. Drug abusers with no antibodies to hepatitis A and hepatitis B should be immunized. Hepatitis A can be fatal in individuals with hepatitis C.

Are there important drug interactions between antiretrovirals and medications for drug treatment?

A common problem in treating patients with HIV who are drug users is the drug interactions between medications. Studies have shown that interactions of methadone and antiretroviral medications are linked to CYP450 3A4 sites in the liver. The most significant interactions are between methadone and nevirapine (NVP) or efavirenz (EFV), which precipitate rapid drug withdrawal symptoms (see Table 13-7). Methadone programs should be alerted when methadone patients are started on efavirenz or nevirapine, as dose escalation of methadone will probably be required. When methadone and didanosine (ddI) are coadministered the uptake of didanosine may be lowered requiring a higher dose of didanosine (See Drug Tables 7 and 8 in the Pocket Guide). Other interactions caused by drugs such as abacavir

(ABC) and all the PIs except indinavir (IDV), though pharmacologically measurable, are not clinically apparent and standard doses are appropriate. Potential interactions between illicit drugs and HIV medications are less well understood. Methamphetamine products have been associated with sudden death in individuals on protease inhibitors. Anecdotal reports describe how selective serotonin reuptake inhibitor (SSRI) antidepressant medications may produce side effects that mimic drug withdrawal and may decrease AIDS medication adherence.

Table 13-7: Antiretroviral Drugs that Affect Methadone Levels

| NRTI | NNRTI | PI |
|---------------------|---------------------|--------------------|
| zidovudine (ZDV) ↔ | nevirapine (NVP) ↓ | indinavir (IDV) ↔ |
| didanosine (ddl) ↔ | delavirdine (DLV) ↑ | ritonavir (RTV) ↓ |
| zalcitabine (ddC) ↔ | efavirenz (EFV) ↓ | nelfinavir (NFV) ↓ |
| stavudine (d4T) ↔ | | saquinavir (SQV) ? |
| abacavir (ABC) ↓ | | amprenavir (APV) ↓ |
| | | lopinavir (LPV) ↓ |
| | | atazanavir (ATV) ↓ |

↓ = decreases methadone blood levels
 ↔ = indeterminate effect
 ↑ = increases methadone blood levels

Source: Adapted from Gourevitch MN, Friedland GH. Interactions between methadone and medications used to treat HIV infection: a review. *Mt Sinai J Med* 2000 67:429-436.

Why are HIV and drug abuse both such noticeable issues now?

HIV and substance abuse are both significant public health problems that merit the attention of public health officials and policymakers. Today, an estimated 40 million people worldwide are living with HIV. Of these, 2 to 3 million people are injection drug users. In the United States, approximately a third of HIV/AIDS cases are related to injection drug use. Research shows that use of drugs, injected or not, can affect decisionmaking – particularly about engaging in unsafe sex – that can endanger the health of the drug user and of others. Substance abuse is a double-edged sword because it increases an individual’s risks for continuing drug use while also increasing the likelihood of exposure to HIV and other bloodborne infections. Infectious diseases that are more prevalent among injection drug users than in the general population are HIV, other STDs, including hepatitis B and C, and tuberculosis. Prevention and early treatment of drug abuse and drug-related diseases are critical public health measures to reduce the spread of new infections.

KEY POINTS

Substance abuse and addiction involve compulsive drug-seeking behavior that interferes with an individual's ability to function normally in many aspects of daily life. Substance abuse and mental health problems often occur together and, unless treated, can lead to chronic social and medical consequences.

Accurate and reliable diagnosis of substance abuse or dependence is not a perfect science. Screening techniques, in concert with a thorough medical history and evaluation, are important in detecting and correctly diagnosing a substance abuse-related disorder.

HIV transmission is preventable in people who use drugs. For drug users and the community at large, drug addiction treatment is disease prevention.

Hepatitis C is extremely common in patients with a past or current history of injection drug use. All patients with hepatitis C should be vaccinated against hepatitis A and B if serologic studies show no prior exposure.

The clinical issues to be addressed are to treat comorbid conditions as soon as possible, treat drug use and HIV aggressively, and be aware of common drug interactions seen in patients treated for drug use and HIV simultaneously.



SUGGESTED RESOURCES

Brief Interventions and Brief Therapies for Substance Abuse. Treatment Improvement Protocol (TIP) Series 34. Rockville, MD: Substance Abuse and Mental Health Services Administration Center for Substance Abuse Treatment; 1999. DHHS Publication No. (SMA) 99-3353. Available at <http://www.health.org/govpubs/BKD341/> Accessed 1/04.

Klein MB, Lalonde RG, Suissa S. The impact of hepatitis C virus coinfection on HIV progression before and after highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2003;33:365-372.



WEBSITES

American Society of Addiction Medicine: <http://www.asam.org/> Accessed 11/03.

National Institute on Drug Abuse: <http://www.nida.nih.gov> Accessed 11/03.

Erowid (detailed biochemical and other information on drugs): <http://www.erowid.org> Accessed 11/03.

Office on National Drug Control Policy: <http://www.whitehousedrugpolicy.gov/> Accessed 11/03.

Substance Abuse and Mental Health Services Administration (drug abuse statistics, clinical treatment information): <http://www.samhsa.gov> Accessed 11/03.

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Principles of Drug Addiction Treatment: A Research-Based Guide. Bethesda, MD: National Institute on Drug Abuse; 1999. NIH Publication 99-4180. Available at <http://www.drugabuse.gov/PubCat/PubsIndex.html> Accessed 1/04.

Principles of HIV Prevention in Drug-Using Populations: A Research-Based Guide. Bethesda, MD: National Institute on Drug Abuse; 2002. NIH publication 02-4733. Available at <http://www.drugabuse.gov/PubCat/PubsIndex.html> Accessed 1/04.

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Chapter 14:

Mental Health Disorders

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OVERVIEW

DISORDERS OF ATTENTION OR COGNITION

PERSONALITY DISORDERS

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OVERVIEW

Why is it important to address mental health disorders in persons living with HIV?

HIV infection increases the risk of developing psychiatric disorders, including depression, mania, psychosis, and substance abuse (Treisman, 1999). For patients with preexisting mental illness, a diagnosis of HIV can significantly impact their ability to cope with HIV disease, adhere to treatment regimens, and take advantage of support networks and care systems, and can result in deterioration in their quality of life. Individuals with previous histories of mood, cognitive, or anxiety disorders may exhibit a reemergence or exacerbation of symptoms. As persons with HIV/AIDS live longer and the focus of care shifts from acute to chronic, the long-term psychological impact of HIV disease becomes more apparent.

What common HIV-related medical conditions have psychiatric symptoms?

It is essential for primary care providers to be aware of the need for a comprehensive evaluation of psychiatric symptoms in persons with HIV disease. Many psychiatric symptoms can indicate an underlying opportunistic disease or other condition (see Table 14-1).

What are the most common mistakes made in mental health management of HIV-infected patients?

Primary care providers commonly 1) under-diagnose depression, 2) under-dose antidepressant medications, 3) neglect substance use management and treatment, 4) stigmatize patients with psychiatric disorders, and 5) assume that psychotherapy implies a lengthy and detailed conversation.

Table 14-1. HIV-Related Conditions That Can Present With Psychiatric Symptoms

| Type of problem | Condition |
|--------------------------------|---|
| Opportunistic brain infections | Toxoplasmosis, cryptococcal meningitis, cytomegalovirus infection, tuberculosis, progressive multifocal leukoencephalopathy, neurosyphilis |
| Opportunistic malignancies | Lymphoma, Kaposi sarcoma |
| Metabolic complications | Fever, anemia, blood infections, hypoxia, hypotestosteronism |
| Drug toxicity | Corticosteroids, alpha-interferon, efavirenz (EFV) |
| Substance abuse complications | Recreational drugs (cocaine, alcohol, methamphetamine, hallucinogens, nitrate inhalant, opiates) Prescribed drugs (benzodiazepines, opiates, psychostimulants) |

What conditions warrant psychiatric consultation?

Providers should obtain psychiatric consultation in 1) major depression refractory to medication trials, 2) bipolar disorder, 3) schizophrenia, and 4) suicidal or homicidal thoughts.

DISORDERS OF ATTENTION OR COGNITION

What are the characteristics of delirium in patients with HIV infection?

Delirium, which is a state of global derangement of cerebral function, occurs more frequently in medically

ill, brain injured, or metabolically unstable patients. The clinical presentation and the differential diagnosis in HIV patients are the same as in HIV noninfected individuals, with the additional possibility that delirium is HIV-related. Presentation may vary in the presence of psychomotor agitation or retardation. Emotional changes are common and often unpredictable, and hallucinations and delusions are frequently seen. Electroencephalography may show diffuse slowing of the background alpha rhythm, which resolves as confusion clears. The syndrome has an acute or sub-acute onset and remits fairly rapidly once the underlying cause is treated.

How do you manage delirium in patients with HIV infection?

Non-pharmacologic treatments include identification and removal of the underlying cause, reorientation of the patient (calendars, clocks, view of outside world, and active engagement with staff members), and pharmacologic management of behavior or psychosis. Low doses of high-potency antipsychotic agents such as haloperidol are often useful. Newer, atypical antipsychotics are currently being used with some success, but those with more anticholinergic activity may worsen the condition. Benzodiazepines should be used cautiously, as they may contribute to delirium in some patients, except in cases of alcohol or benzodiazepine withdrawal deliria. Physical restraint should be used as little as possible as it often worsens delirium.

How do you diagnose and treat minor cognitive-motor disorder (MCMD)?

MCMD is a less severe neurocognitive disorder of earlier HIV infection, and the symptoms are often overlooked because they may be very subtle. Cognitive and motor slowing are most prominent and are often discovered as a result of a minor complaint, such as taking longer to read a novel, dysfunction when performing fine motor tasks, or an increased tendency to stumble. Diagnosis is made by the finding of 2 or more of the following symptoms for more than a month: impaired attention and concentration, mental slowing, impaired memory, slowed movements, lack of coordination, and changes in personality (irritability or emotional lability). Some patients continue to have minor problems, while others progress to frank dementia. Antiretroviral therapy (ART) may be of some benefit in slowing progression, but this conclusion is confounded by a lack of understanding of factors that lead some patients to progress while others remain static.

How do you diagnose and treat HIV-associated dementia?

HIV-associated dementia presents with the typical triad of symptoms seen in other subcortical dementias—memory and psychomotor speed impairments, depressive symptoms, and movement disorders. Initially, patients may notice slight problems with reading, comprehension, memory, and mathematical skills. Patients later develop global dementia, with marked impairments in naming, language, and praxis. Clouding of consciousness is absent, and there is no evidence of another cause. Motor symptoms are often subtle in early stages, including occasional stumbling while walking or running, slowing of fine repetitive movements, and slight tremor. There may be impaired saccadic eye movements, dysdiadochokinesia, and hyperreflexia. Apathy is also a common early symptom, often causing noticeable withdrawal from social activity. A frank depressive syndrome also commonly develops, typically with irritable mood and anhedonia instead of sadness and crying spells. Sleep disturbances are quite common, as is weight loss. Psychosis may develop in a significant number of patients and generally presents with paranoid beliefs, although hallucinations may exist. In 5%-8% of patients, a syndrome known as AIDS mania develops in addition to the HIV-associated dementia. In later stages, there may be frontal release signs and rather severe motor symptoms, including marked difficulty in smooth limb movements, especially in the lower extremities.

HIV dementia is typically seen in late stages of illness, usually in patients who have had a CD4 count nadir of < 200 cells/mm³. Certain risk factors have been associated with eventual development of HIV dementia, namely, higher HIV RNA viral load, lower education level, older age, anemia, illicit drug use, and female sex. Prognosis is rather poor, with a rapidly progressive nature, usually ending in death within 2 years.

Standard of care is to ensure an optimal ART regimen and treat associated symptoms aggressively. Depression can be treated with standard antidepressants, and in some cases methylphenidate or other stimulants may be useful in the treatment of apathy. Safety assessments should be performed as with any other case of dementing illness.

What is the relationship between psychosis and HIV?

Psychosis, including schizophrenia, contributes to behaviors that may lead to HIV infection, including higher rates of injection drug use, unprotected sex,

multiple sex partners, trading sex for money or other goods, and sex while intoxicated (Cournos et al, 1994). Providers who see patients with psychosis should be sensitive to the risk of acquiring HIV and should screen patients carefully for risk behaviors.

Accumulating evidence suggests that HIV infection may be directly linked to the onset of psychosis. Psychosis can be a manifestation of delirium, affective disorders, or schizophrenia, but can it occur in the absence of these conditions. Estimates of the prevalence of new-onset psychosis in patients with HIV range from 0.5%-15%, which is higher than in the general population (Kendler et al, 1996; Sewell et al, 1994). New-onset psychosis may also be a manifestation of HIV-associated encephalopathy. History of substance abuse also is more common among patients with psychosis.

How do you treat HIV-infected patients with schizophrenia?

The principles of treatment for HIV-infected patients with schizophrenia follow the same basic principles as for any other patient with schizophrenia, namely, control of symptoms with medications and psychosocial support and rehabilitation. Quite often, patients require long-term treatment and require various antipsychotic medications to control the delusions, hallucinations, and overall level of disorganization.

PERSONALITY DISORDERS

What is the relationship between personality disorders and HIV infection?

Personality disorders represent extremes of normal personality characteristics and are disabling conditions. Clinical observation suggests that patients with personality disorders who are highly extroverted and highly neurotic are most prone to engage in HIV risk behavior. These individuals are preoccupied by and act upon their feelings, and their actions tend to be unpredictable and inconsistent. Past experience and future consequences have little salience in decisionmaking for individuals who are ruled by feeling; the present is paramount. Their overarching goal is to achieve immediate pleasure or removal of pain, regardless of circumstances. Patients are more fixed upon the reward of sex and remarkably inattentive to the STDs they may acquire. In addition, substance abuse is more likely a comorbidity with these patients. Injection drug use is markedly more common because

the experience is much more intense and pleasurable. Thus, patients with personality disorders are at risk for HIV infection, and if they are already HIV-positive they are at risk for transmitting HIV to others. Management of patients with personality disorders includes encouraging a focus on thoughts rather than feelings, use of a behavioral contract, emphasis on constructive rewards, use of relapse prevention strategies, and coordination with additional health and psychosocial care providers.

MOOD DISORDERS

What are characteristics of adjustment disorders in patients with HIV?

Adjustment disorders are common emotional responses to HIV and often account for the “hopeful highs” and “helpless lows” experienced by some patients. These reactions are typically situational and transient, but reflect significant distress in the patient. Adjustment issues vary according to a variety of factors in addition to stage of illness, risk factors, socioeconomic status, level of education, characteristics of support networks, and comorbid psychiatric disorders. Adjustment reactions are most likely to occur at the time of significant medical events, especially during transition points in the illness. These conditions typically are accompanied by less severe depression and/or anxiety than are classic mood disorders. Treatment is usually non-pharmacologic and includes promotion of a structured environment, reassurance, engagement of the patient in the treatment process, close monitoring for progression of symptoms, and supportive counseling and psychotherapy.

How do you diagnose bipolar disorder in patients with HIV?

Bipolar disorder, also known as manic-depressive illness, is a condition in which patients classically alternate between extended episodes of depression and briefer periods of hypomania or mania with increased mood, increased energy, increased confidence, and grandiose ideas. Manic episodes are associated with increased rates of substance abuse and impulsive behavior, and there has been speculation that bipolar disorder may be a risk factor for HIV infection. AIDS-related mania appears to be specifically associated with late-stage HIV infection and is associated with cognitive impairment and a lack of previous episodes or family

history. The history will usually reveal progressive cognitive decline prior to the onset of mania. Irritable mood is more typical than euphoria, and prominent psychomotor slowing may replace the expected hyperactivity of mania, complicating the diagnosis. The presentation is usually quite severe in its course. AIDS mania appears to be more characteristically chronic, has few spontaneous remissions, and readily relapses with cessation of treatment (Lyketsos et al, 1997).

How do you treat bipolar disorder in patients with HIV?

The treatment of mania in early-stage HIV infection is responsive to mood stabilizing medications, particularly lithium, valproic acid, and carbamazepine. Antipsychotic agents, particularly atypical agents, are often utilized in the acute phase as well. These medications decrease manic symptoms and may prevent recurrence. Treatment strategies may be somewhat different in advanced HIV disease. AIDS mania may respond to treatment with antipsychotics alone. In general, patients are often exquisitely sensitive to dosage changes that might otherwise seem trivial. Few data exist for the newer anticonvulsants such as gabapentin and lamotrigine, and these medications should be used sparingly. The major problem with lithium in AIDS patients has been rapid fluctuations in blood level, even when on previously stable doses. Lithium intoxication is not uncommon in this setting. Valproic acid has been successfully used when titrating to usual therapeutic serum levels of 50-100 ng/dL. Hepatotoxicity may significantly limit treatment, particularly in the setting of chronic viral hepatitis or severe hepatic *Mycobacterium avium* complex infiltration. Hematopoietic abnormalities may also occur, requiring close monitoring of white blood cell and platelet levels. Carbamazepine may be effective but is poorly tolerated because of sedation and potential for bone marrow suppression in combination with antiviral medications and viral burden. Patients with late-stage HIV are also significantly affected by toxic side effects of antipsychotic medications, and a much lower dosage may be required than in other settings.

How do you diagnose major depressive disorder in patients with HIV?

Several lines of evidence suggest that HIV is a causal factor in depression, and that depression is a causal factor in HIV-related morbidity (Ciesla and Roberts, 2001). Differentiating appropriate sadness from pathologic depression may be difficult in the person infected with HIV. Psychomotor retardation and apathy of AIDS dementia complex may be confused with

depression, but will often improve in patients who are on combination antiretroviral treatment. Organic mood disorders may also have symptoms similar to major depression and are responsive to antidepressant medication.

Depression is underrecognized, underdiagnosed, and undertreated (see Table 14-2). At the same time, it is important for providers to consider alternative diagnostic possibilities for depressive symptomatology (see Table 14-3).

Table 14-2. Risk Factors for Depression

| |
|--|
| History of prior mood disorder |
| History of substance abuse or active substance use |
| Prior suicide attempt |
| History of anxiety disorder |
| Family history of depression or suicide |
| Inadequate social support |
| Nondisclosure of HIV status |
| Multiple losses |
| Advancing illness |
| Treatment failure |

Table 14-3. Differential Diagnosis of Major Depression

| |
|--|
| Nonpathologic states of grief and mourning |
| Dysthymia |
| Delirium |
| Dementia |
| Demoralization |
| Substance intoxication |
| Substance withdrawal |
| CNS injury or infection |
| Acute medical illness |

What are the pharmacologic treatment options for major depression?

Pharmacotherapy is the mainstay of treatment for major depression (see Table 14-4). No single antidepressant has been found to be superior in treating HIV-infected patients as a group. Patient adherence to regimens is critical, and those who take adequate doses of antidepressants have the best chance of improving. A general rule is to start with low doses of any medication, titrating up to a full dose slowly, in order to minimize early side effects that may act as obstacles to adherence.

Table 14-4. Medications to Treat Depression in HIV Disease

| Medication | Starting dose | Usual therapeutic dose | Serum level | Advantages | Interactions with HIV medications |
|--------------------------|----------------------|--|--------------------|---|---|
| nortriptyline (Pamelor) | 10-25 mg qhs | 50-150 mg qhs | 70-125 ng/dL | Promotes sleep, weight gain, decreases diarrhea | Fluconazole, lopinavir/ritonavir, and ritonavir increase nortriptyline levels. |
| desipramine (Norpramin) | 10-25 mg qhs | 50-200 mg qhs | >125 ng/dL | Promotes sleep, weight gain, decreases diarrhea | Lopinavir/ritonavir and ritonavir increase desipramine levels. |
| imipramine (Tofranil) | 10-25 mg qhs | 100-300 mg qhs | >225 ng/dL | Promotes sleep, weight gain, decreases diarrhea | Lopinavir/ritonavir and ritonavir increase imipramine levels. |
| amitriptyline (Elavil) | 10-25 mg qhs | 100-300 mg qhs | 200-250 ng/dL | Promotes sleep, weight gain, decreases diarrhea | Lopinavir/ritonavir and ritonavir increase amitriptyline levels. |
| clomipramine (Anafranil) | 25 mg qhs | 100-200 mg qhs | 150-400 ng/dL | Promotes sleep, weight gain, decreases diarrhea | Lopinavir/ritonavir and ritonavir increase clomipramine levels. |
| doxepin (Sinequan) | 10-25 mg qhs | 150-250 mg qhs | 100-250 ng/dL | Promotes sleep, weight gain, decreases diarrhea | lopinavir/ritonavir and ritonavir increase doxepin levels. |
| fluoxetine (Prozac) | 10 mg qam | 20 mg qam | unclear | Activating, energizing | Amprenavir, delavirdine, efavirenz, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, and saquinavir increase HIV medication levels. Nevirapine decreases fluoxetine levels. |
| sertraline (Zoloft) | 25-50 mg qam | 50-150 mg qam | unclear | | Lopinavir/ritonavir and ritonavir increase sertraline levels. |
| citalopram (Celexa) | 20 mg qam | 20-60 mg qam | unclear | | Lopinavir/ritonavir and ritonavir increase citalopram levels. |
| paroxetine (Paxil) | 10 mg qhs | 20-40 mg qhs | unclear | Mildly sedating | Lopinavir/ritonavir and ritonavir increase paroxetine levels. |
| fluvoxamine (Luvox) | 50 mg qhs | 150-250 mg qhs | unclear | Mildly sedating | Amprenavir, delavirdine, efavirenz, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir and saquinavir increase HIV medication levels. Nevirapine decreases fluvoxamine levels. |
| venlafaxine (Effexor) | 37.5 mg qam | 75-300 mg qam | unclear | | Lopinavir/ritonavir and ritonavir increase venlafaxine levels. |
| mirtazepine (Remeron) | 7.5-15 mg qhs | 15-45 mg qhs | unclear | Promotes sleep, weight gain | |
| nefazodone (Serzone) | 50 mg bid | 300-400 mg/d in divided doses | unclear | Mildly sedating | Efavirenz and indinavir increase HIV medication levels. |
| trazodone (Desyrel) | 50-100 mg qhs | 50-150 mg qhs for sleep 200-600 mg qhs for depression | unclear | Promotes sleep | Lopinavir/ritonavir and ritonavir increase trazodone levels. |
| bupropion (Wellbutrin) | 100 mg qam | 150-400 mg/d in divided doses | unclear | Activating, no sexual side effects | |

The first week of treatment usually determines whether a patient will be able to tolerate the medication at all. Following this period, the dosage should be increased slowly to either a typical therapeutic dose or serum level, when appropriate. Patients should be encouraged to wait as long as possible for the therapeutic effect, which may take at least 6 weeks to achieve. Close monitoring for side effects should be done at every visit, and the side effects treated whenever possible. For example, insomnia because of selective serotonin reuptake inhibitor (SSRI) use may respond well to low doses of trazodone. Constipation from tricyclic antidepressants is often relieved by increasing water and fiber intake. Sexual side effects from SSRIs are common and may be treated with sildenafil in some, or by drug holidays, switching to bupropion, and addition of buspirone, cyproheptadine, or ginkgo biloba.

For patients showing only partial response to antidepressant medications after an adequate trial period, several other agents are often useful for augmentation strategies. The best studied is lithium, yet its side-effect profile often prevents use in the HIV setting. Olanzapine, risperidone, and pindolol have also been reported to be effective augmenting agents, as well as addition of a second antidepressant, other mood stabilizers, trazodone, methylphenidate, benzodiazepines, sleep deprivation, and phototherapy.

If no benefit is gained from the primary antidepressant, even after augmentation, a new primary agent should be chosen and similarly titrated slowly, and augmented if necessary. There is evidence to suggest that a response may be seen from 1 drug where none was seen from another in the same class.

What are the nonpharmacologic treatments for major depression?

Psychotherapy is an integral part of the treatment of major depression. Treatment with medication plus psychotherapy has been shown to be more effective for patients than either modality alone. Patients often require education about the disease nature of their depression, encouragement, and therapeutic optimism that the treatments will work. Medical providers who keep the concept of psychotherapy in mind will structure their interactions with patients to slowly empower and enable the patients to take control of their lives, thus relying on their providers less and less.

ANXIETY DISORDERS

How do you diagnose anxiety disorder in patients with HIV infection?

Anxiety disorder, which can include generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, and post-traumatic stress disorder, is a common response to the stressors of HIV infection at any stage. True anxiety disorders tend to be less prevalent than depressive disorders, particularly at later stages of HIV infection. Anxiety is often a component of major depression, and further history should be ascertained for patients presenting with symptoms of panic or anxiety. Anxiety may also be due to substance use, and neurologic and physical impairment.

What are pharmacologic treatments for HIV-infected patients with anxiety?

Physicians must aggressively screen for major depression in patients presenting with anxiety symptoms, because both conditions often coexist. In particular, anxiety is a frequent symptom of major depression. Antidepressant medications are very effective in most cases.

In particularly debilitating cases, however, anxiolytic medications can be used for time-limited intervention and in low doses. Exclusion of patients with comorbid substance abuse is essential prior to initiation of anxiolytic medication, because of the abuse liability. Medications with a short half-life should be very cautiously used, as dependence may easily develop over a short period of usage. Particular attention should be given to the issues of hepatic function and choice of anxiolytic. Lorazepam, oxazepam, and temazepam avoid hepatic glucuronide conjugation by means of an alternate metabolic pathway and should be chosen as first-line medications for patients with HIV-associated liver dysfunction, as in patients with viral hepatitis.

What are nonpharmacologic treatments for HIV-infected patients with anxiety?

Specific advantages to utilizing nonpharmacologic intervention for anxiety include a decrease in pill burden, decrease in CNS sedation and cognitive impairment, lack of drug-drug interaction, and avoiding polypharmacy. Some interventions are 1) muscle relaxation, 2) meditation techniques, 3) psychotherapy, 4) exercise, 5) biofeedback, 6) behavioral techniques, 7) guided imagery, and 8) cognitive therapy.



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Chapter 15:

Palliative and End-of-Life Care

Carla S. Alexander, MD
Kennita R. Carter, MD

INCORPORATING PALLIATIVE CARE INTO HIV CARE
CARE AT THE END OF LIFE
KEY POINTS
SUGGESTED RESOURCES
REFERENCES

INCORPORATING PALLIATIVE CARE INTO HIV CARE

What is palliative care?

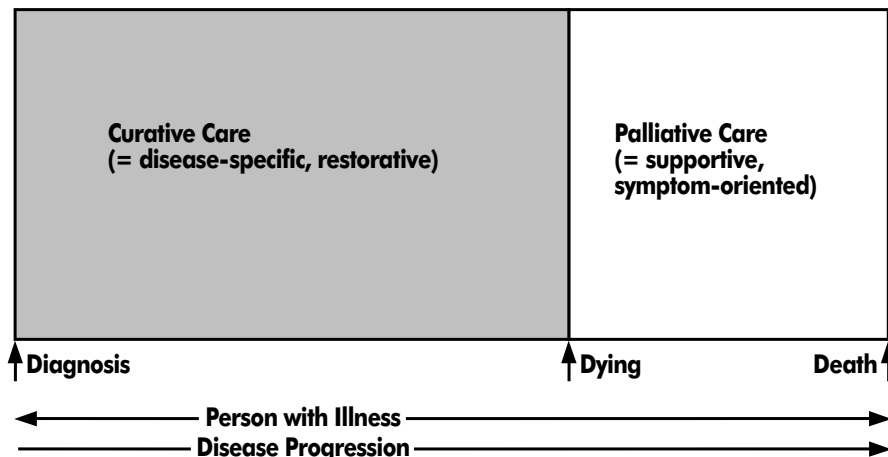
Palliative medicine is the discipline devoted to the relief of suffering and the promotion of quality of life. Palliative, meaning non curative, has often been misunderstood to be limited to end-of-life or hospice care; it is rather a more general term for the type of supportive care needed throughout the trajectory of any chronic illness or major injury.

In traditional medical care, efforts are primarily curative or restorative until a poorly defined point when provider and patient acknowledge disease progression and decide to shift toward less aggressive management (See Figure 15-1a). In chronic progressive illnesses supportive care might be provided simultaneously assuring maximum quality of life throughout the course of illness for patients, family and caregivers (Figure 15-1b).

Why is palliative care still needed for people with HIV/AIDS, now that antiretroviral therapy (ART) is so successful?

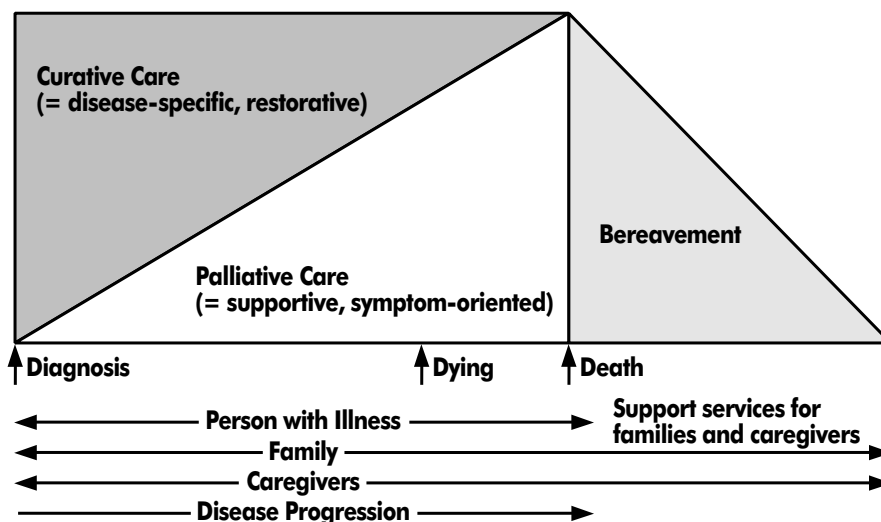
AIDS, originally considered a terminal illness, has transitioned to a chronic disease for those who are able to use ART. However, there is still a steady death rate in the United States of 15,000 to 16,000 per year. While the numbers are low compared with the epidemic in the early years, persons living with HIV disease continue to experience pain, body habitus changes, and other physical and emotional symptoms that negatively impact their daily quality of life. Preventing and controlling these problems are as relevant as reducing viral load. Setting realistic goals and improving self-esteem allow the person with HIV disease to remain in control of his/her life and to be a productive member of society.

Figure 15-1a: Traditional Model of Care (first curative, then palliative)



Source: World Health Organization. *Cancer Pain Relief and Palliative Care, Report of a WHO Expert Committee.* Publication #1100804. Geneva: World Health Organization, 1990.

Figure 15-1b: Integrated Model of Care (curative and palliative together)



Source: World Health Organization. *Cancer Pain Relief and Palliative Care, Report of a WHO Expert Committee*. Publication #1100804. Geneva: World Health Organization, 1990.

What does palliative care focus on?

The following are essential elements of palliative care:

- Goals of care are patient- and family-driven and frequently revised.
- Relationships with an interdisciplinary team provide the mechanism for care.
- Truth-telling and support for realistic decisionmaking are the norm.
- Aggressive prevention and control of bothersome symptoms are paramount.
- It is understood that psychosocial, emotional, and spiritual needs significantly impact symptoms.
- Integration of a palliative care approach throughout the disease trajectory improves quality of life.
- Early identification of and communication with a proxy decisionmaker is a priority.
- Evaluation and treatment decisions are modified based upon prognosis.
- Near the end of life, unnecessary drugs are eliminated and comfort measures provided.
- Assisting the dying person to achieve psychosocial and spiritual closure is a goal of care.
- Family and friends are provided with care techniques and communication skills.
- Care of the caregiver and of the provider are essential aspects of providing supportive care.

- Legal, ethical, and cultural aspects are acknowledged and respected.
- It is recognized that dying is an inevitable part of life, not an enemy to be denied.
- Anticipatory grieving and bereavement support for the family are included in care.

How can palliative care be incorporated into primary HIV care?

A palliative approach to HIV disease management begins by obtaining an accurate assessment of the patient's support system, life goals, and preferences early in the disease process. Then the following activities are incorporated into the care plan:

- Open appraisal of stage of disease with appropriate goal setting
- Yearly review of goals (more frequently if symptomatic)
- Anticipation of and prophylaxis for side effects of ART
- Education regarding advance care planning well before patient is symptomatic
- Use of standardized questionnaires to assess presence of symptoms and their impact on quality of life
- Provision of separate medical appointments to manage symptoms such as pain or weight loss

- Reduction of diagnostic studies and number of medications as prognosis shortens
- Regular review of health power of attorney and support of patient wishes
- Discussions of prognosis with patient and family soon enough to allow closure near the end of life
- Referral to hospice/palliative home care when office visits become burdensome for patient
- Maintenance of contact with family during bereavement period
- Acknowledgement of staff members' feelings of loss when patients die

What are some common symptoms experienced by persons with advanced HIV disease?

In surveys, patients receiving ART report experiencing the same symptoms as patients reported in the earlier years of the epidemic, but the frequencies of symptoms have changed (Mathews et al, 2000; Vogl et al, 1998). Fatigue, sadness, diarrhea, and fever continue to plague patients even when disease is controlled by ART. Pain is still experienced by up to 75% of patients and may be present in multiple areas at once, including the extremities and oral, esophageal, abdominal, or rectal sites. Adequate treatment for one type of pain may only expose another. This often raises the specter of “drug-seeking behavior” when in fact the patient is simply able to be aware of the secondary pain after the greater pain is relieved (see Chapter 13, Management of Substance Abuse). Peripheral neuropathy can be caused by ART, HIV disease itself, or unrelated disease such as diabetes. This pain does not seem to be related to the degree of control of viral burden, and cause must be sought through historytaking as many patients seem to overlook early manifestations such as numbness. Refer to Chapter 8, Symptom Management, as well as resources under Suggested Resources for management of pain and symptoms.

How important is pain control in advanced HIV disease?

Pain, as with any symptom, should be described, quantitated, treated, and promptly reevaluated with appropriate dose modification of therapy (see Table 15-1). In the *Guidelines for Management of Cancer Pain*, pain experienced by those with HIV disease is compared with the chronic pain experienced by persons with cancer, which often requires management with opioids (AHCPR, 1994). Unlike blood pressure, which might be regulated over weeks, pain should be controlled within the shortest time possible to prevent the development of long-term symptoms such as depression and anhedonia.

Table 15-1. Mnemonic for Assessment of Pain

| | |
|----------|---|
| A | A sk about pain regularly; A ssess systematically |
| B | B elieve the patient and family |
| C | C hoose treatment options appropriate to patient and setting |
| D | D eliver medications on an “around-the-clock” basis with adequate “breakthrough” doses |
| E | E valuate results frequently; E mpower patients and families to control pain |

The following guidelines are helpful in prescribing pain medication (American Pain Society, 1999):

1. Use a grading system (such as the scale of 0–10) to document pain severity and compare the number obtained to a second number following treatment to evaluate response.
2. Start with a dose that will acutely relieve the pain. This may be given intravenously or subcutaneously to achieve a rapid response. Care should be taken to observe for any signs of respiratory depression in opiate-naive patients who receive parenteral opioids.
3. Next, begin a low dose every 3–4 hours (based on the half-life of the drug) “around-the-clock,” **not** on an as-needed, basis. The initial dose should be chosen based on the age, size, and renal/hepatic function of the patient. (See Suggested Resources for additional guidance on pain management.)
4. A “breakthrough dose” should also be prescribed every 1-2 hours prn equal to a sixth of the total daily opioid dose. This allows for development of a steady state drug level and avoids alternation of great pain intensity with somnolence. This is the same approach used to control hyperglycemia with a sliding scale of regular insulin based on glucometer readings; doses are based on pain scores.
5. When pain is fairly well controlled, it is appropriate to change the patient to a long-acting pain medication for ease of administration. The dose is calculated by adding together the total dose taken in 24 hours and dividing by the half-life of the new preparation. For example, for a medication meant to be given every 12 hours: divide the total dose by 2, and this number will be the dose every 12 hours. Don't forget the breakthrough dose. This is a short-acting opioid, preferably of the same type as the long-acting one for use at times when the pain is not adequately controlled.
6. Other forms of administration include liquid formulations for persons with difficulty swallowing, rectal suppositories, “sprinkles” that can be mixed with soft food, and patches that allow absorption of the medication through the skin.

What is advance care planning?

Advance care planning is an attempt to clarify patient wishes near the end of life. Identification of a “health care proxy,” a person who makes decisions if the patient becomes unable to communicate his or her own wishes, should be encouraged and documented in the medical record with contact information. Even when formal directives have not been written the patient should discuss his or her thoughts and concerns about the end of life with that person. Hosting a family meeting to discuss the issues might also be useful. A “living will” may be difficult to write because it is not possible to anticipate every event that might occur when one is critically ill. It may be better for the person to clarify general thoughts about the use of ventilators or other intensive support mechanisms for sustaining life. Permanency planning should be included in this discussion whenever children are involved.

Family members feel inadequate when confronted with end-of-life decisionmaking. Realistic guidance provided to the health care proxy can minimize that emotional burden (see Table 15-2). The provider should discuss in detail what a resuscitation effort means and give a specific description of what might happen during the use of “life supports” (eg, one cannot talk and may not be able to communicate when on a respirator; the combination of early dementia and an episode of hypoxia might result in significant diminution of mental capacities).

What is hospice care?

Hospice can be a philosophy, a place, a type of home care, or a reimbursement mechanism (EPEC Curriculum, 2003). The goal of hospice care is to reduce suffering by controlling symptoms, consolidating medications, and supporting the patient and family in living fully until death. However, in the United States obtaining hospice care for any individual often depends on insurance coverage. For a person on Medicare a referral to hospice care requires that the patient have a life expectancy of less than 6 months if the disease runs its normal course. This is a complex determination in any chronic illness. Patients who have decided to forego restorative therapy or who no longer want to be admitted to a hospital are not the norm in HIV disease, but working with a local hospice program may make this transition less burdensome. For financial reasons the patient may be offered “palliative” rather than “hospice” care.

Table 15-2. Useful Questions for Exploring Patient and/or Family Concerns

| Domain | Question |
|---|---|
| Physical comfort | Tell me about your pain. Can you rate it on a 10-point scale? |
| | How much do you suffer from physical symptoms like shortness of breath, fatigue, or bowel problems? |
| Continuity with one's self | What makes life most worth living for you at this time? |
| | If you were to die sooner rather than later, what would be left undone? |
| Maintaining and enhancing relationships | How are your family (or loved ones) handling your illness? |
| | Have you had a chance to tell your family (or loved ones) how they are important to you? |
| Making meaning of life and death | What kind of legacy do you want to leave behind? |
| | What would allow you to feel that going through this illness has a purpose? |
| | Do you have spiritual beliefs that are important in how you deal with this illness? |
| Achieving a sense of control | How would you like your death to go? |
| Confronting and preparing for death | How much are you thinking about dying now? What are you thinking about it? |

Source: Alexander C, Back A, Perrone M. Medical Care at the End of Life. In O'Neill JF, Selwyn PA, Schietinger H, eds. *A Clinical Guide to Supportive and Palliative Care for HIV/AIDS*. Rockville MD: Health Resources and Services Administration. 2003.

CARE AT THE END OF LIFE

What are the challenges of end-of-life care for the provider?

Deciding when to make the transition from curative/restorative mode to one of comfort measures only and having the skills to communicate this to the patient are probably the greatest challenges facing the provider (see Table 15-3). While guidelines exist for having difficult conversations effectively, avoiding conveying

a message of abandonment is the real difficulty. Being adept at managing symptoms such as pain can give the provider confidence when initiating this conversation. Reassuring the patient and family that comfort measures are always possible and isolating one problem at a time may minimize their sense of being overwhelmed. Simply asking the patient what goals are important helps refocus on concrete issues that can be successfully mastered.

Another significant challenge for the provider may be foregoing invasive diagnostic studies when the patient is moving closer to death. The astute practitioner needs to rely on physical assessment and knowledge of probabilities to surmise the cause of a symptom. Using one medication for multiple outcomes minimizes pill burden. For example, steroids may be employed for relief from dyspnea; this same drug might also improve appetite and sense of well-being, suppress fever, and relieve achiness related to prolonged bedrest.

| Table 15-3. Mnemonic for Breaking Bad News | |
|---|--|
| S | S etting and listening S kills |
| P | P atient and family P erception of condition |
| I | I nvitation to patient to determine how much I nformation he/she wants to know |
| K | K nowledge; reviewing the facts |
| E | E xplore E motions and E mpathize |
| S | S ummary & S trategy |

Source: Adapted from Baile W, Buckman R. *Practical Guide to Communication Skills in Clinical Practice*. Niagara Falls, NY: Medical Audio Visual Communications, Inc, 1998.

What roles do culture and spirituality play in end-of-life care?

Culture and spirituality are significant factors affecting how end-of-life care should be delivered to each individual patient and family. Lack of clarification of cross-cultural differences can be a barrier to patients' receiving appropriate end-of-life care. Spirituality, connection with a higher power, or a sense of meaning can provide tremendous comfort and support. Not recognizing these issues or the impact of AIDS-related stigma might even add to suffering. It is useful to ask the patient if he/she has a faith and how important it is to him/her. If the provider does not feel comfortable

addressing these issues, every attempt should be made to have someone on staff or for easy referral to address this need. It has been clearly documented in medical literature that spiritual concerns might be involved in exacerbation of all types of illness.

How do you provide reality-based hope for the person with advanced AIDS?

Hope is an intrinsic value that allows the human spirit to persevere even against great difficulty. When a person is nearing the end of life, it may not be reasonable to want to live until a certain birthday that will not occur for several months. In this case, the health care staff needs to help with a redefinition of hope that is more achievable. Some families in hospice programs have celebrated religious holidays a month ahead of time, held ceremonies before they were originally scheduled, and made videotapes of the dying person to be played during an up-coming event.

How do you conduct a family meeting?

Prior to a family meeting, the provider must prepare a mental agenda to identify internal and external barriers to achieving a clear and therapeutic picture of the goals important to all involved (see Table 15-4).

What does the patient need to accomplish before death?

There are multiple physical, psychosocial, and spiritual issues that deserve attention in order for the patient to die peacefully and to leave satisfactory memories for family and friends. The patient and family need to:

- Appoint a health power of attorney and talk with that person about support preferences
- Make a will to avoid conflict following death, including guardianship issues
- Attempt to resolve previous misunderstandings or estrangements
- Encourage family and friends to openly discuss the patient's deterioration to avoid a "conspiracy of silence"
- Express love and appreciation to family, friends, and staff
- Engage family, friends, and staff in a life review (eg, telling stories about accomplishments, regrets, funny things that have happened along the way)
- Create a memory book or video tape, or write letters for children left behind
- Discuss plans or preferences regarding funeral or memorial service
- Say goodbye to family, friends, and caregivers (the patient needs reassurance that those left behind will be cared for and that he or she will be remembered)

Table 15-4. Components of a Discussion about End-of-life Care

| |
|---|
| <p>I. Making preparations prior to a discussion about end-of-life care:</p> <ul style="list-style-type: none"> Review previous knowledge of the patient and/or their significant others Review previous knowledge of the patient's attitudes and reactions Review your knowledge of the disease prognosis, treatment options Examine your own personal feelings, attitudes, biases, and grieving Plan the specifics of location and setting: a quiet, private place Have advance discussion with the patient or family about who will be present |
| <p>II. Holding a discussion about end-of-life care:</p> <ul style="list-style-type: none"> Introduce everyone present If appropriate, set the tone in a non-threatening way: "This is a conversation I have with all my patients..." Find out what the patient or significant other understands Find out how much the patient or significant other wants to know Be aware that some patients do not want to discuss end-of-life care Discuss prognosis frankly in a way that is meaningful to the patient Do not discourage all hope Avoid temptation to give too much medical detail Make it clear that withholding life-sustaining treatment is NOT withholding caring Use repetition to show that you understand what the patient or the significant other is saying Acknowledge strong emotions and use reflection to encourage patients or their significant others to talk about these emotions Tolerate silence |
| <p>III. Finishing a discussion of end-of-life care:</p> <ul style="list-style-type: none"> Achieve common understanding of the disease and treatment issues Make a recommendation about treatment Ask if there are any questions Ensure basic followup plan and make sure the patient and/or significant others know how to reach you for questions |

Source: Curtis JR. Patient-Clinician Communication. In O'Neill JF, Selwyn PS, and Schietinger H, Eds. *A Clinical Guide to Supportive and Palliative Care for HIV/AIDS*. Rockville, MD: Health Resources and Services Administration, 2003.

What steps should you take after writing a Do Not Resuscitate (DNR) order?

After writing an order for "No CPR" the provider should reverse these letters to offer family and friends "RPC" - Reassurance, Presence, and Caring. Facilitate conversations that acknowledge the role of family and friends in care. Be present for family even if only briefly. For hospitalized patients, write orders to intervene that assure comfort measures will be provided even when antibiotics or pressors might be discontinued (see Table 15-5).

Table 15-5: Life's End

| | |
|--|---|
| The following mnemonic may be helpful when writing DNR orders: LIFE'S END. This stands for | |
| L | Keep the L ips and mouth moistened with ice chips |
| I | Expect urinary and fecal I ncontinence when patient is too weak to get out of bed; insert a catheter/use bed pad |
| F | Expect F evers and use around-the-clock antipyretics possibly by the rectal route |
| E | Eliminate all but E ssential medications |
| 'S | Be aggressive about S ymptom management |
| E | E ating decreases; substitute other supportive activity for family members who want to continue feeding |
| N | N ursing call orders should be revised |
| D | D ecubitus ulcer prevention requires turning every 2 hours |

Source: Copyright Palliative Care Program, University of Maryland, Baltimore, MD; 1999. Reprinted with permission.

What can the family expect as their loved one is dying?

Many people have little experience with the actual process of dying. At a time when family members feel grief and a loss of control, it is comforting to have a simple description of what to expect as they sit at the bedside. The provider needs to offer this information (see Table 15-6) as well as to suggest activities the family can do to offer comfort and to alleviate their feeling of helplessness.

What must the provider do after the patient dies?

At the time of death, those present need verification that in fact their loved one has died. It is useful to review what has happened and to offer supportive comments to those present as they adjust to this new information. It is comforting for them to remain with the deceased and say their goodbyes. Cultural beliefs will dictate behavior, and it is helpful to have discussed these practices ahead of time. Providers can:

- Reassure the family that they provided good and loving care
- Allow family members to remain at the bedside as long as necessary to bring closure

- In the hospital, place something on the bed to honor the space recently vacated
- Tell family when to expect autopsy findings if autopsy is requested
- If an autopsy is performed, schedule time to discuss this with the family
- Notify other staff members who may have cared for this patient
- Send a condolence card
- Call family 1-2 weeks after the death to listen

| Table 15-6: What the Family Should Expect of the Patient Prior to Death | |
|--|--|
| 1–2 weeks prior to death | <ul style="list-style-type: none"> • <i>Withdrawal from people</i> • <i>Decreased food and liquid intake</i> • <i>Talking with those who are already dead</i> • <i>Sleeping longer periods</i> • <i>Picking at clothing</i> • <i>Feeling very fatigued</i> |
| Days to hours prior to death | <ul style="list-style-type: none"> • <i>Surge of energy; seems like “himself”</i> • <i>Cheyne-Stokes respirations</i> • <i>Decreased urine output</i> • <i>Acral and large joint cyanosis</i> • <i>“Death rattle”</i> • <i>Weak pulse and decreased blood pressure</i> |

Source: Adapted from Kearnes, *Gone from My Sight*. Depoe Bay OR: BK Books; 1995.

How can a primary care practice or clinic avoid staff burnout when several of the patients have died?

Providers who suffer from the death of more than one patient over a short time period may experience symptoms of multiple loss syndrome which, if unattended, can lead to symptoms found in post-traumatic stress disorder. They need to take the time to effectively grieve. How this is accomplished is a personal matter for each individual, but the clinic or health care facility must recognize the importance of allowing each person to come to a sense of closure after a patient’s death. For some, attending the wake or funeral may be helpful. For others, a clinic-based time for remembering the individual(s) can provide a structured outlet for feelings of grief.

The focus of providers tends to be on caring for others. Primary care providers often have not received formal training in preventing and identifying burnout. With an ever increasing work load and shrinking time for office visits and administrative responsibilities it is easy to miss signs of stress (see Table 15-7). O’Neill and McKinney describe a 2-pronged approach to preventing and managing burnout. This involves developing more effective individual coping skills as well as creating a less stressful work environment (O’Neill and McKinney, 2003). Examples of personal coping strategies include: 1) being mindful of eating, exercise, and sleep patterns, 2) keeping a daily journal to record the events that cause stress, and 3) discussing personal experiences with someone else. A less stressful work environment includes a choice of mechanisms for ‘taking a break’ from the steady emotional drain of patient care.

| Table 15-7: Common Signs of Stress for Caregivers | | |
|--|---|---|
| Physical | Psychological | Behavioral |
| Backaches | Anger and frustration | Emotional outbursts |
| Change in eating patterns | Loss of self-confidence and self-esteem | Withdrawal from friends and family |
| Diarrhea | Loss of interest in and commitment to work | Loss of punctuality and neglect of duty |
| Elevated blood pressure | Feelings of inadequacy, helplessness, and guilt | Decrease in judgmental ability |
| Fatigue | Feelings of restlessness | Inability to focus on tasks |
| Gastrointestinal problems | Depression | Tearfulness |
| Headaches | Sense of being overwhelmed or overloaded | Increased use of alcohol or other drugs |
| Insomnia | Mood swings | Difficulty getting along with people |
| Muscle tension | Sense of failure | Impaired work performance |
| Weight loss | Anxiety about the future | Resistance to change |

Source: O’Neill JF, McKinney M. Caring for the caregiver. O’Neill JF, Selwyn PA, and Schietinger H, Eds. *The Clinical Guide to Supportive and Palliative Care for HIV/AIDS*. Rockville, MD: Health Resources and Services Administration, 2003.

KEY POINTS

Palliative medicine is the discipline devoted to the relief of suffering and the promotion of quality of life. Palliative care has often been thought to be limited to end-of-life or hospice care; it is rather a more general term for the type of supportive care needed throughout the trajectory of HIV disease.

Advance care planning is an attempt to identify a decisionmaker should the patient become unable to communicate his or her own wishes.

Deciding when to make the transition from curative/restorative mode to one of comfort measures only and having the skills to communicate this to the patient are probably the greatest challenges facing the provider.

There are multiple physical, psychosocial, and spiritual issues that need resolution in order for the patient to die peacefully and to leave satisfactory memories for family and friends.

The focus of providers tends to be on caring for others. Providers who suffer from the death of more than one patient over a short time period can experience symptoms of post-traumatic stress disorder. They need to take the time to effectively grieve.



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Chapter 16:

Clinic Management

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PATIENT RECRUITMENT AND RETENTION

CLINICAL SERVICES NEEDED FOR HIV CARE

SUPPORT SERVICES AND LINKAGES NEEDED FOR HIV CARE

KEY POINTS

SUGGESTED RESOURCES

PATIENT RECRUITMENT AND RETENTION

How can primary care clinics recruit patients with HIV into care?

The persons who were easy to recruit and retain in care are already enrolled; the more challenging patients await recruitment. Every clinic should 1) be linked to agencies providing HIV testing and services for persons with HIV and 2) make clinic access easy for the clients of those outside services.

Many clinics establish referral linkages with community services that provide HIV counseling and testing services (CTS), AIDS service organizations (ASOs), STD treatment facilities, family planning agencies, drug treatment facilities, local health departments, regional HIV/AIDS hotlines, and local hospitals and emergency rooms. Many clinics also offer free confidential or anonymous CTS using State or Federal funding.

Clinic personnel should build personal relationships with agencies that may provide referrals, invite staff of community agencies to visit the clinic, or hold an open house. Providers from ASOs, such as case managers, can be invited to accompany patients on clinic visits. Referring agencies must know what services the clinic provides and which patients it serves, as well as those it cannot serve. Clinics with Ryan White Care Act (RWCA) funding should be able to accept patients regardless of health insurance or ability to pay. Primary care clinics can benefit from having a brochure describing their programs and array of services, along with information about making appointments, hours of service, and so forth.

Clinics differ based on the characteristics of the people living in their catchment area and the expertise of clinic staff. Some successful clinics target a narrow but underserved population and concentrate on

meeting the needs of that population. A youth-friendly environment may differ from one targeting the working poor.

How do clinics retain patients in care?

Respect, cultural competence: Respecting patients and providing them with effective care builds trust and keeps them coming back. New clinic attendees may have strong feelings related to HIV infection (fear of death) or how they acquired it (issues of shame or of secrecy). They may lack trust in medical care (prior personal experiences or the legacy of the Tuskegee syphilis experiments) or in current treatments (“Everyone I knew who took AZT died...”). Patients encounter barriers where there are cultural differences or language barriers between themselves and the staff. Staff members should be trained to anticipate, recognize, and work with these issues.

Welcoming staff attitude: Patients should always be made to feel that they came to the right place (even when it is not true, and they must be referred on). Patients should receive understanding and support, even when they arrive in clinic without obtaining the required managed care referral form (at least the first few visits). Providers must know the target population and build a system that will make patients feel welcome. Many RWCA-funded clinics employ patient advocates, persons from the target community who may or may not themselves be HIV-infected. Advocates directly assist patients in negotiating the clinical care system and help patients ask questions or make their needs known to clinical staff. Advocates or peer support persons can be instrumental in helping patients build self-esteem and acquire new habits that will enable them to use health care services in a proactive manner. It is very helpful for patients to be able to forge a personal connection with at least one staff member.

Welcoming environment: Physically comfortable waiting and examination areas, with linguistically and culturally appropriate decoration and reading material, are important for patient retention. A clinic that serves parents or children should make available toys or children's books.

Orientation to clinic systems and rules: New patients need a brief description of clinic staff and services, routine and emergency procedures, prescription refill procedures, and after-hours followup. They must understand about requirements for referrals from managed care providers, and new patients may need help with such requirements. Patients must also be oriented to what is expected of them (eg, coming on time, calling to cancel or reschedule appointments) and the consequences of not fulfilling their responsibilities (eg, clinic rules regarding late arrivals). A handout or pamphlet with staff names, clinic hours and phone numbers, and emergency procedures can be very helpful.

Systems to support attendance: Patients should receive reminders (by phone or mail) about 48 hours before each appointment. It is also useful to have a staff member contact patients who have missed appointments to find out what prevented them from attending and offer to reschedule. ASOs may have funding for transportation (eg, door-to-door taxi service for selected patients, van service, vouchers for use on public transportation). Other barriers may require a coordinated effort by the clinic staff, case manager, and others. Clinic sessions should be scheduled at times convenient for the patients; mid-to-late afternoon is best for school-age children, occasional evenings or weekends are good for working people.

CLINICAL SERVICES NEEDED FOR HIV CARE

What is the optimum array of services that an HIV clinic should provide?

All patients with HIV need a similar array of services that must be provided either directly or through referral. Patients need providers knowledgeable in the diagnosis and treatment of HIV infection and its complications, including state-of-the-art use of antiretroviral therapy (ART). Services must address the clinical conditions associated with patients' current or prior risk behaviors. Given improved life expectancy, patients need age-appropriate general preventive and screening services. The high rates of premorbid mental health problems in persons with HIV and mental health problems related

to HIV disease make mental health services a key component of HIV care. Substance abuse treatment is crucial. Confronting the epidemic by including HIV prevention activities in clinical care sites is a new activity, challenging and critically important (see Chapter 4).

The HIV/AIDS Bureau of the Health Services and Resources Administration (HRSA) lists basic services required for agencies to receive funding through the RWCA Title III (Early Intervention/Primary Care) Program (Table 16-1). Some States have produced more detailed lists for agencies wishing to receive special State-level funding for HIV care; see the New York State list for comparison (Table 16-2). Funded programs generally must demonstrate continuity in primary care, 24-hour access to emergency care, ongoing staff training, an administrative apparatus adequate to manage the program and its funding, a reporting system to meet the grantors' requirements, and quality management. Programs that do not receive explicit funding for clinical care and/or support services need to rely more on referral networks.

Table 16-1: HIV/AIDS Bureau Requirements for Title III-funded Early Intervention/Primary Care Programs

- HIV counseling, testing, and referral
- Counseling and education on living with HIV disease, including availability and use of treatment therapies
- Appropriate medical care and monitoring, including CD4 cell monitoring, viral load testing, antiretroviral therapy, and prophylaxis and treatment of opportunistic infections, malignancies, and other related conditions
- Oral health care, outpatient mental health care, substance abuse treatment, nutritional services, and specialty care either directly or through a formal referral mechanism
- Appropriate referrals for other health services
- Perinatal care including therapy to reduce mother to child transmission (MTCT)
- Screening/treatment of TB

Source: Adapted from Ryan White C.A.R.E. Act Title III Manual. Rockville, MD: HIV/AIDS Bureau, Health Resources and Services Administration. 1999(Section II):5. Available at <http://www.hab.hrsa.gov/CATIE/> Accessed 2/04. Table 16-2. Comprehensive Ambulatory HIV Programs from the New York State AIDS Institute

Monitoring and treating the long-term complications of ART, such as insulin resistance, lipodystrophy syndromes, dyslipidemia, and osteopenia, are of increasing importance. Instituting formal activities to assist patients in behavior change is increasingly recognized as an essential component of HIV care. Hepatitis C diagnosis and management are of particular importance for patients who have had blood product

exposures or who were drug injectors. Screening for premalignant human papillomavirus (HPV) disease in men using anal Pap smears is potentially valuable, although it has not become a universal standard of practice.

Clinics should also have a system in place to protect the safety of their employees in regard to occupational HIV exposure (See Chapter 10 as well as Suggested Resources below).

| Table 16-2. Comprehensive Ambulatory HIV Program Standards of the New York State AIDS Institute | |
|---|--|
| Clinical services that must be provided by ambulatory HIV programs | |
| On site | |
| <ul style="list-style-type: none"> • Age appropriate, confidential HIV counseling and testing • Initial and annual comprehensive medical evaluations, including substance abuse and mental health assessments • Cognitive function testing • Ongoing clinical HIV disease monitoring • HIV-specific therapies and prophylactic treatments, including treatment education and adherence monitoring • Routine gynecologic care and followup (including reproductive counseling, pelvic examinations, and Pap smears) • Routine family planning services • Case management • Patient health education, including risk reduction and nutrition counseling | |
| On site or via linkage | |
| <ul style="list-style-type: none"> • Access to consultations by specialists in infectious diseases • Core diagnostic and therapeutic services <ul style="list-style-type: none"> - laboratory, including early diagnostic methods to establish the infection status of children - radiology, including MRI - pharmacy - dental services - mental health services, including clinical social work, clinical psychology, and psychiatry as clinically appropriate • Other primary care, specialty, and subspecialty services <ul style="list-style-type: none"> - obstetrics - pediatrics, adolescent medicine, and pediatric subspecialties - ophthalmology - dermatology - outpatient surgery - clinical pharmacy - subspecialties of internal medicine, including gastroenterology, hematology, pulmonology, and oncology | |

Source: New York State AIDS Institute. Comprehensive Ambulatory HIV Program Standards. Part 490 of Title 10 NYCRR. November 1994.

What is different about providing HIV care compared with other types of medical care?

HIV care is new; the epidemic was recognized in 1981, and potent therapy became available in 1996. Therapeutic options are much improved, but there is little room for error. Drug resistance may occur rapidly and is irreversible. The ongoing development of new therapeutic agents is impressive, yet is not rapid enough to ensure future therapies to persons who received inappropriate prescriptions, or who did not receive the requisite education, support, and counseling to succeed with their therapy. With therapies that have been in use for less than 10 years, much is still unknown about long-term outcomes.

Juxtaposed against the need for expertise in HIV care is the need to expand access. The only prerequisite to developing expertise in HIV care is commitment. A wide range of providers may be the HIV experts for their communities: midlevel practitioners and physicians, generalists and subspecialists. Providing infected persons with the tools to succeed in their treatment and to avoid future HIV transmission may require stepwise behavior change. A persistent and nonjudgmental approach is most likely to be effective (for more on adherence see Chapter 7). Providers may have to change their own behaviors so they can be more effective in patient care.

Most persons receiving HIV care reduce their transmission behaviors, lowering the risk of HIV infection for others. Others do not change their behaviors, or do so only partially, or relapse. Providing prevention interventions in a clinic protects the public health. Clinic staff may know sex and drug using partners of patients, and find themselves with a duty to warn those who may be unknowingly exposed. These issues will be familiar to those in tuberculosis and STD treatment settings; but for many these challenges are new (see Chapter 4 on HIV prevention and Chapter 13 on substance abuse).

HIV/AIDS is associated with discrimination and stigma because of its association with sexual behavior and with drug injection, and because HIV is incurable and may still be eventually fatal. Historically, there has been discrimination because of fear of contagion based on misconceptions regarding transmission. Discrimination may still be encountered in families and communities experiencing HIV for the first time.

What can clinics do to ensure that patients receive the necessary array of services?

Clinic forms can be designed to remind providers of care standards, simplify data collection, and serve other purposes as well. Sample forms for initial and followup visits are posted on the HRSA HIV/AIDS Bureau (HAB) website (<http://www.hab.hrsa.gov>). They include reminders regarding clinical standards, reminders of services required for billing levels, checklists built around definitions used by RWCA grantees for reporting to HRSA, and other data for quality management. Staff members may rebel when confronted with new forms; however, using checklists often saves time by listing required elements of the visit and by reducing the amount of writing. Including clinical, data, and quality management staff in the process of designing forms eases the transition.

Information systems can produce reports useful to providers, for example listing a patient's prior diagnoses, medications, and sequential plasma HIV RNA levels and CD4 cell counts (see again the HAB website for examples). Similar flow sheets can be generated from electronic medical record systems; some commercial services also provide such services, but confidentiality must be assured. Periodic reports of achievement of clinical standards (viral load targets, opportunistic infection prophylaxis, vaccination, cancer screening, and other health maintenance activities) can easily be provided to individual providers, and to the clinic medical director, linking implementation of the chronic care model (see Chapter 1) and quality management (see Chapter 17).

What enhancements can make an HIV clinic more effective?

Clinics can enable patients to better care for themselves by providing them with information about HIV and by building a community among them. Patients should be given education materials; a separate area with HIV-related materials may help maintain confidentiality. Some clinics display male and female condoms with instructions about their use and have available other information on safer sex and birth control. Much information is available for patients, including publications on medications, side effects, and adherence. Free materials are available from Federal and State web sites, and the pharmaceutical industry also produces some excellent materials.

Many ASOs and clinics host support groups for interested patients. Participation must be voluntary, and only patients comfortable with revealing their status

to other patients will be willing to participate. Some groups target specific populations. Groups may be more successful if an experienced counselor or mental health provider leads them.

Some clinics hold classes on HIV and adherence. Clinics serving pregnant women and parents may include classes on birth preparation and parenting. Other clinics provide periodic symposia to keep patients up-to-date on treatment advances. For clinics that have a community advisory board, the board can be the organizing force for these community updates. Both public grants and the pharmaceutical industry support these events.

Some youth-oriented clinics arrange social events and outings for their patients. Some programs for children or mothers provide support services for both infected and affected children, ranging from formal psychological care to supportive recreational activities after school or during school breaks.

How can clinics implement interdisciplinary care?

It is not enough to have staff from many disciplines on the payroll; rather, systems have to be created that allow staff to function as a team. Training with followup by supervisors is essential. Specific tasks of each staff member need to be assigned (Table 16-3). Ideally, the staff can meet for a few minutes prior to each clinic session to anticipate special needs and allocate personnel resources. Some clinics place a checklist on each chart at each visit, to indicate which team members a patient is meant to see that day and to confirm that all intended interactions have occurred.

The team's potential can best be utilized if there is a regular opportunity to meet and discuss patients outside of clinic sessions, often called multidisciplinary team meetings. When all members participate, the discussions can range from selecting antiretroviral regimens based on genotype or phenotype results for one patient to addressing chronic mental illness for another. Services for infected and affected family members can be coordinated at these sessions.

Should clinics have a stated policy regarding controlled drugs?

Controlled drugs are needed as part of comprehensive care of HIV-infected patients, for treatment of psychiatric conditions and pain. At the same time, many patients with HIV have had prior or have current issues with substance abuse. The clinic should have policies in place regarding prescription of controlled

medications: how many prescription refills are provided at a time, how new refills are provided, access to controlled drug prescriptions or refills outside of normal clinic hours, and refills of lost medication or lost prescriptions. To avoid confusion or disagreement some clinics have patients sign copies of the clinic policy regarding use of controlled medications before they are given prescriptions. It may be necessary to provide formal notification to a substance abuse program or parole officer that the clinic is prescribing a controlled medication, specifying the drug, dose, and duration of treatment.

| Table 16-3. Clinic Staff Responsibilities |
|--|
| Tasks prior to a clinic visit |
| <ul style="list-style-type: none"> • Remind every patient of appointments via phone call or postcard • Review charts to list items to address during the visit |
| Tasks during a clinic visit |
| <ul style="list-style-type: none"> • Verify patient's current contact information and current insurance status • Orient new patients • Assist with insurance gaps (teaching about need for referrals, help with insurance application or ADAP, etc) • Assess other barriers to care and psychosocial needs • Assess medication adherence • Teach and provide behavior change counseling about medications and self-care • Assess ongoing transmission behaviors • Teach and provide behavior change counseling about transmission behaviors • Educate about clinical trial opportunities (if applicable) • Make referrals for psychosocial services • Make referrals/appointments for medical, dental, mental health care |
| Tasks following clinic sessions |
| <ul style="list-style-type: none"> • Make followup calls regarding new medication regimens or referrals • Call or mail postcards to patients who miss their visits • Help patients overcome barriers to clinic attendance • Extract data and enter it into the information system (not necessary with electronic medical records) |

SUPPORT SERVICES AND LINKAGES NEEDED FOR HIV CARE

How do support services enhance the clinical care of persons with HIV?

It is a rare clinic that has the funding, personnel, and expertise to address all of its patients' psychosocial issues. Most patients need services from an array of agencies. Case managers assist patients in accessing the range of services and entitlements that can help them succeed in treatment. This includes assistance in applying for insurance; accessing support groups; accessing supplemental food, housing, homemaker and other concrete services; accessing mental health and substance abuse services. Case managers should perform periodic assessments of clients' needs and update comprehensive care plans every 6 months. Home visits can be very useful as part of the assessment. Some case managers or their agencies will provide selected direct services themselves; these may include short-term counseling, transportation for clinic visits, accompanying patients to clinic visits, and providing financial assistance for specific emergencies. Excellent case managers help motivate patients.

Close coordination between clinic staff and case management is important to avoid duplication of effort and services. Periodic case conferences between clinic staff and case managers are ideal. Written communication, for example sharing case management care plans, can be useful. Case management agencies and clinical sites need to obtain written consent from patients to share the information that allows coordination.

How do clinics create useful linkages with community-based services?

Clinics can develop relationships with community-based case managers or directly with providers of specific services, such as mental health, substance abuse, or housing. Personal contact between clinic and agency is important to establish the relationship, and ongoing contacts are necessary for coordination. Community organizations are often pleased to give in-service education to clinic staff in order to streamline the referral process. Clinics should make their expectations clear to community-based agencies. Clinics can function as advocates to ensure that their patients receive the attention and services for which they were referred. Periodic interdisciplinary meetings of clinic staff with representatives of community-based agencies, including case managers, are very useful.

How should consumers be involved in the provision of HIV clinical care?

Many clinics have created consumer advisory boards to participate in planning and quality management. Experiences have varied greatly, with some advisory board members educating themselves about the issues and providing expert input to these processes. Other boards act more as social event or support groups. Clinics are likely to have to train board members in technical background regarding HIV and care provision, and in the role of advisors. Board members must agree to confidentiality policies, even though information about individual patients or staff members should not be discussed. Clinics have to create meaningful opportunities for advisory board members to provide input: this may involve discussion of workplans in writing grant applications, planning outreach activities, modifying clinics to enhance recruitment and retention of patients, and participating in quality management teams. When consumers are living in poverty or otherwise difficult conditions, obtaining ongoing participation of volunteers may require providing transportation to meetings, meals at meetings, and reimbursement for childcare or similar expenses. Some clinics find it useful to pay officers of their advisory boards in order to enable the officers to devote adequate amounts of time to the project. If this seems contradictory to the spirit of volunteerism, we should remember how much continuing education of medical and nursing professionals relies on enhancements to recruit participation. Creating effective advisory boards takes time, but can be a valuable investment. Advisory board members, while providing an outside view of the clinic to the clinic management, often provide useful community outreach and improve public relations.

Less intensive consumer input involves the use of periodic satisfaction surveys or questionnaires of clinic patients, confidential or anonymous mechanisms for eliciting suggestions, and a publicly accessible grievance procedure. Clinics with advisory boards use these mechanisms as well.

What resources are required to provide comprehensive HIV/AIDS care?

Financial: Patient access is maximized in clinics that can accept Medicare, Medicaid (including Medicaid managed care), and county insurance programs. Clinics should have a sliding fee scale. Clinics should assist appropriate patients to enroll in the AIDS Drug Assistance Program (ADAP), to access the drug coverage or other clinical services that vary by State.

Within designated metropolitan areas, RWCA Title I funding may be available. Clinics planning to serve a moderate-to-high volume of HIV patients can apply for a RWCA Title III planning grant. Clinics serving women, pregnant women, youth, and families are eligible to apply for Title IV funding. Clinics may collaborate with other agencies in seeking RWCA funding.

Personnel: A lone provider whose patients are self-sufficient or can access community-based services can “provide” comprehensive HIV/AIDS care. For most patients, care is more effective if multiple team members are available at the clinical site.

Facilities: In addition to the usual office layout, other facilities are useful. An examination room suitable for gynecologic exams is important. An apparatus for pulse oximetry is very useful in assessing patients with respiratory symptoms. Easy access to facilities for collecting venous blood, urine, and stool specimens should be available. On-site access to rapid tests that do not require CLIA certification may be useful, such as urine pregnancy tests, capillary blood glucose, and perhaps the newly licensed rapid whole blood HIV antibody screening test. Laboratory certification to perform urine analysis and microscopic examination of vaginal fluid specimens is very useful. Refrigeration to maintain vaccines and material for tuberculin skin testing is necessary. Refrigeration also enables the clinic to provide patients with on-site injection of medications required once a week or less frequently and to instruct patients in the use of more frequent injections.

Training and technical assistance: Patients look to nontechnical staff to corroborate information given by physicians and midlevel providers. Further, patients expect the same accepting attitude from all staff members. Thus, all staff need training in both technical and cultural matters. One important resource is the local performance site of the AIDS Education and Training Center (AETC) funded by HRSA to provide training and technical assistance to clinics. The local AETC and the National Clinicians’ Consultation Warmline provide detailed and patient-specific education to assist clinicians in making treatment decisions. Written educational materials for staff, such as national and regional treatment guidelines, are available free on the web and are frequently updated. Many regional and national meetings provide training in both clinical care and prevention. Assistance with enhancing and implementing systems of care, including instituting a quality management program, is also available from the AETCs. Chapter 18 provides other resources for training and information.

KEY POINTS

In order to recruit persons with HIV who are not in care, clinics need to establish referral linkages with community agencies such as HIV testing services, AIDS service organizations that provide case management, STD and drug abuse treatment facilities, family planning agencies, local health departments, regional HIV/AIDS hotlines, and local hospitals and emergency rooms.

Clinics can retain patients in care by respecting patients, providing them with effective care, and addressing cultural and language differences between patients and staff. Providing a welcoming staff attitude and physical environment are also important.

Orienting patients to the clinic systems and rules and telling them what is expected of them can improve attendance and adherence to care.

Primary care clinics must be able to provide, either directly or through referral, an array of clinical and psychosocial services that includes mental health and substance abuse services, support for HIV prevention and adherence to care, and close medical monitoring. Some issues that differ in HIV disease from other medical conditions include that there is little room for error in providing treatment, that providers may need to change their own behaviors and attitudes to provide effective care, that preventing HIV transmission is a critical component of patient care, and that patients continue to suffer discrimination and stigma.

Patient services can be enhanced in primary care clinics through the introduction of mechanisms for reminding staff of clinical standards, simplifying data collection, and monitoring quality improvement. These can include forms, checklists, and flowsheets, on paper or in electronic databases, and can result in feedback such as reports to individual providers. In addition, educational materials and support activities for patients can enhance their care.

An interdisciplinary care team, which is an important component of HIV primary care services, can be developed by creating systems for staff collaboration and communication, such as training, assignment of tasks with checklists on patient charts designating responsible team members, and multidisciplinary team meetings at which the issues of individual patients are discussed.

Resources needed to provide comprehensive HIV care include the capacity to accept Medicare, Medicaid, and county insurance programs and access to the AIDS Drug Assistance Program for coverage of antiretroviral drugs. In addition, the Ryan White Care Act makes a variety of funding programs available for direct funding to clinics for care. Ongoing training and technical assistance are critical to keep the expertise of staff up to date.



SUGGESTED RESOURCES

National HIV/AIDS Clinicians' Consultation Center (Free and confidential advice from a multidisciplinary team)

Warmline: 1-800-933-3413
Monday-Friday, 9 am to 8 pm EST

PEP Hotline: 1-800-448-4911
24 hours a day/7 days a week

Website: <http://www.ucsf.edu/hivcntr>
Accessed 2/04.

HIV/AIDS Bureau: <http://www.hab.hrsa.gov>
Accessed 4/04 (An array of technical assistance tools for clinic management are available at this HRSA website)

Chapter 17:

Quality Improvement

Bruce D. Agins, MD, MPH

OVERVIEW
DATA COLLECTION
KEY POINTS

SUGGESTED RESOURCES
REFERENCES

“Quality of care is the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.”

(Institute of Medicine, 1990)

“All health care organizations, professional groups, and private and public purchasers should pursue six major aims; specifically, health care should be safe, effective, patient-centered, timely, efficient, and equitable.”

(Institute of Medicine, 2001)

OVERVIEW

Quality Improvement: Why Bother?

An open letter to clinic directors:

You may have dismissed quality improvement from your agenda for many reasons. You may think it is someone else’s job, or it’s a lot of extra work with no benefit, or think that you’ve already got a quality program in place. You may think that your current system of monitoring the charts in your clinic and giving feedback to the providers who aren’t doing the right thing is a quality improvement (QI) program. You may also think that your clinic is doing a fantastic job and that you don’t need to monitor its quality. Here’s why it’s worth investing the time and effort:

- Data generated from your QI program showing improvements over time demonstrate that the program is worth its funding
- QI provides an opportunity to solve problems that are part of the system and not dependent on one individual
- Focus on performance measurement and improvement usually stimulates employees to maximize their performance
- Clinicians have the opportunity to provide leadership through championing best outcomes for patient care
- Innovative problem-solving techniques lead to better care and promote a positive working environment
- QI projects demonstrate compliance with accreditation authorities and grant sponsors
- Quality improvement activities that lead to better outcomes provide a competitive edge when competing for alliances with purchasers
- Monitoring systems that are dependent on single individuals will not last when these key players leave the clinic or are absent for long periods, whereas a fully functioning quality improvement program that involves staff working in teams with a clearly defined infrastructure will keep going when even the most dynamic individuals depart.

This chapter describes how your clinic can develop, implement, and maintain a QI Program and what your role in it might be, whether part of a QI Project Team, the Quality Committee, or simply a customer of the performance measurement and quality improvement processes.



What is Quality Improvement (QI)?

Quality improvement (QI) includes regular measurement of care processes and outcomes to analyze processes and systems of care. It involves implementation of solutions to improve care and monitor their effectiveness with the goal of achieving optimal health outcomes for patients. Ongoing cycles of change and remeasurement are implemented to test and try different ideas to determine which result in improved care. QI activities in clinics can range from a single team focusing on improving one aspect of care to a comprehensive QI program with many teams working on a wide variety of improvement projects, with a well-established plan and an oversight committee.

The methods of QI are based on core principles that are readily translated into a practical approach and integrated into the clinical care delivery system (see Table 17-1). Successful implementation of QI involves actions at 2 different levels: the QI activities and the HIV program processes that provide the structural backbone for them. This section will articulate the core principles and describe activities that can be easily adapted into the HIV ambulatory care setting to implement a sustainable QI program.

Table 17-1: Core Principles of Quality Improvement

- *Focus on the customer: improvement activities result in improved patient health*
- *Measurement: collect and use data to improve care*
- *Emphasis on systems of care: improve processes that link to desired outcomes*
- *Involvement of participants: encourage direct participation in teams by those individuals who implement the processes being evaluated*

Descriptions of the chronic care model that serves as an important application of QI principles to HIV care can be found in Chapter 1, Figure 1-1, and Chapter 18, the section on Integrating HIV Specialty into Practice. A training manual developed from an HIV/AIDS collaborative is available from the Institute for Healthcare Improvement (see Suggested Resources).

Why aren't chart audits sufficient for QI – Why can't management just conduct QI?

Measurement alone is not sufficient to improve quality. A common pitfall in implementing QI programs is to rely solely upon performance data, the medical or program director's interpretation of it, and one person's decisions about how to make changes. Successful improvements

most often result when staff members from the systems being assessed work together in teams. When they are engaged in the process, they are more likely to generate ideas to try and to accept changes.

Which personnel should be involved in QI?

The size of the clinic will determine who participates in quality-of-care activities. In small HIV clinics with a primary care provider, case manager, nurse, and support staff, most of the staff are involved in all aspects of QI work. Larger institutions usually establish an HIV Quality Committee that includes senior management staff of the HIV clinic, designated QI staff if there are any, and other key players who work in the clinic. A member of this committee represents the group in the agency-wide quality committee. The Quality Committee identifies the priorities for improvement or agrees to use priorities identified by staff or patients in the clinic. The Quality Committee also charters improvement teams, identifying potential members who are key stakeholders in the process under investigation or their representatives.

Who should be on the teams?

Teams are formed to address the specific care processes or systems undergoing improvement. Team members should be selected to represent the different functions involved in these processes or to represent the components of the system under focus. The size of a team varies according to the size of the clinic and the process under study. In small clinics, the few dedicated HIV program staff may constitute the project teams, with added representation from different departments as needed, such as from the lab, or from other medical disciplines. In larger clinics, teams often include 6-10 members. Membership should include representatives from the different groups in the clinic who are involved in the care process. In addition to the clinical and case management representatives, scheduling clerks and medical records staff are often important representatives, especially when followup appointments and documentation are important components of the care process or have been identified as areas that need to be improved.

What are the responsibilities of the team?

Teams are expected to identify areas of change, implement pilots to test the change, review data assessing the change, and ultimately make recommendations about improvements. Team meetings should be kept flexible and adapt to the working environment of the clinic as much as possible, although a few specific guidelines will help keep things running

smoothly. These include designating a leader for the team, developing clear and specific aims and goals, and ensuring that a clear line of accountability is defined pointing back up to the Quality Committee. Sometimes, short impromptu meetings keep the momentum of the project going and enable rapid decisionmaking based on results as soon as they become available.

As the Project Team conducts its work and gains experience, it will become more independent and assume more responsibility for ongoing measurement, data collection, and implementation of steps toward improvement.

DATA COLLECTION

How do you select which components of care should be measured?

Indicators are measurable aspects of care that evaluate the extent to which a facility provides a certain element of care. Indicators should be based on standards or guidelines, meet the primary goals of QI, and reflect priorities specific to the community and the clinic. For example, in HIV clinics where the population includes a large number of women, indicators may include rates of routine Pap smears, rates of preconception counseling, or other aspects of care specific to women. In clinics that care for a high volume of patients with severe immunosuppression and advanced HIV disease, indicators may include rates of prophylaxis for specific opportunistic infections, such as PCP and MAC. Some indicators should be selected by soliciting input from patients who attend the clinic (see Table 17-2). Staff members also often know what aspects of care would benefit from being measured and improved and should be consulted to determine priorities. If routine data collection systems already exist in the clinic, data should be reviewed to determine which components of care would be prime candidates for improvement (see Table 17-3 for sample indicators).

Table 17-2: Methods for Obtaining Input from Patients

- Suggestion box
- Surveys
- Focus groups
- Consumer advisory board

Table 17-3: Sample HIV Quality Indicators

| Element Of Care | Quality Of Care Indicator |
|---------------------------|--|
| HIV staging | CD4 cell count test performed every 4 months Viral load measurement test performed every 4 months |
| Antiretroviral therapy | ART drug usage for stable and unstable patients |
| Tuberculosis screening | Annual PPD testing |
| OI prophylaxis | PCP prophylaxis (CD4 count <200 cells/mm ³) MAC prophylaxis (CD4 count <50cells/mm ³) Pneumococcal vaccination |
| Gynecological care | Annual pelvic exam with Pap smear |
| Syphilis screening | Annual syphilis serology |
| Substance abuse education | Annual discussion of substance use Annual discussion of tobacco use |
| Coordination of care | Annual dental exam |

Once the aspect of care has been selected, how do you develop and measure the indicators?

Three major activities constitute the process of indicator development:

- 1) Define the measurement population: location, gender, age, clinical condition, visits.
- 2) Define the measures.
- 3) Develop the data collection plan.

The measurement population is defined by determining the location of care being studied, whether both men and women are eligible, the applicability of the indicator to different age groups, whether any clinical conditions are necessary to determine whether the indicator is applicable, and whether the patient must have been in treatment or visited the clinic more than once.

After defining the population, the measure needs to be defined. For each measure, specific criteria must be developed to define the “yes” response and the “no” response (see Table 17-4). Often this involves deciding during which time period an activity has been performed. For example, an indicator measuring viral load monitoring must include the frequency with which that test should be performed. One simple way to construct this measure would be to ask “Was viral load measured within the last 4 months?”

| Table 17-4. Examples of Specific Measures with Definitions of Responses | | |
|---|---|--|
| Measure | Definition of measure | Yes/No response |
| TB screening (Eligibility: HIV-infected patients without a history of previous TB treatment or a history of a positive PPD) | Was PPD testing performed (placed and read within 72 hours) in the past 12 months? | Yes: PPD screening was performed (placed and read) No: PPD screening was not performed (or it was placed but results were not documented) |
| PCP prophylaxis | Did the patient with <200 CD4 cells/mm ³ and no sustained CD4 cell increase to >200/mm ³ during the last 6 months of the review period receive PCP prophylaxis? | Yes: The patient received PCP prophylaxis No: The patient did not receive PCP prophylaxis |

The data collection plan includes determining the source of information, such as whether medical records or an electronic database will be used, how the data will be recorded, who will record the data, and how a sample will be selected. A representative sample will allow inferences to be made about the clinic population based on observations of the smaller sample. Some form of random sampling should be used, either from a random numbers table, or a selection of every nth record from the list of eligible patients.

A common pitfall at this point is to think of the measurement sample as a research project. For the purposes of QI, a sample just needs to be current, representative, and readily obtained (ie, sample size calculations and the achievement of statistically significant results are not necessary).

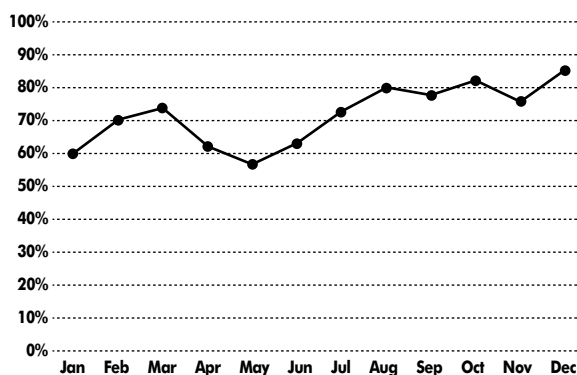
Should you measure only one indicator at a time?

Definitely not. Several indicators should be measured simultaneously, whether abstracted from medical records or analyzed through administrative databases. Indicators reflecting different aspects of patient management should be selected, as well as those involving different populations. Indicators should also be selected to evaluate different components of the health care system, such as the different components of the chronic disease model.

How should you analyze and display data?

Data should be reviewed and distributed to all members of the team and others involved in the care process under evaluation. Whenever possible, data should be displayed in graphic format. Once data from several time periods have been collected (eg, rates of patients with viral load performed every 4 months collected in 2 different time periods), a simple line graph (run chart) can be constructed with each point representing a performance rate (percentage) for a given period of time. This is usually the simplest and most effective way to show performance data (see Figure 17-1).

Figure 17-1: Sample Run Chart: Percentage of Patients PPD Tested, by Month

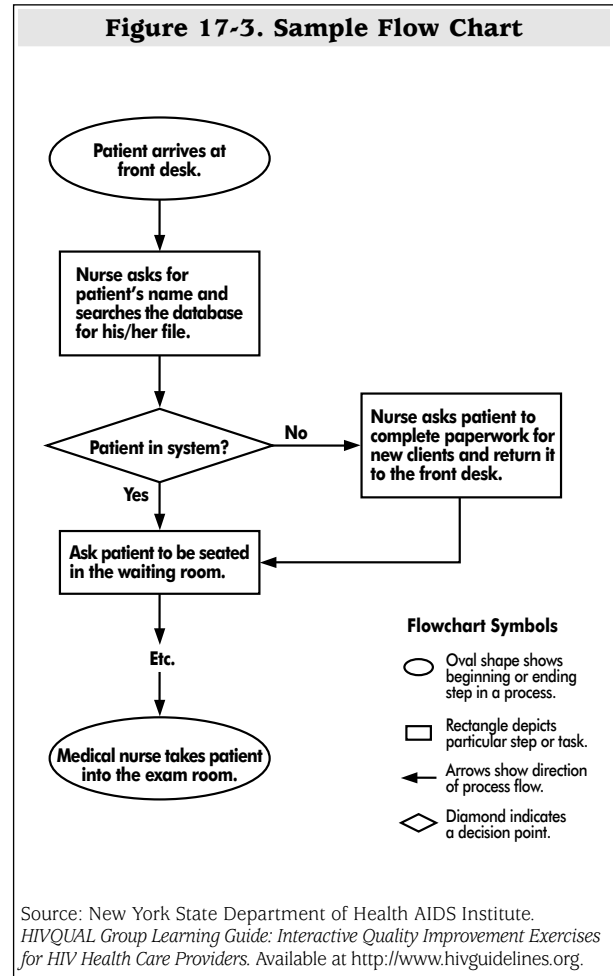
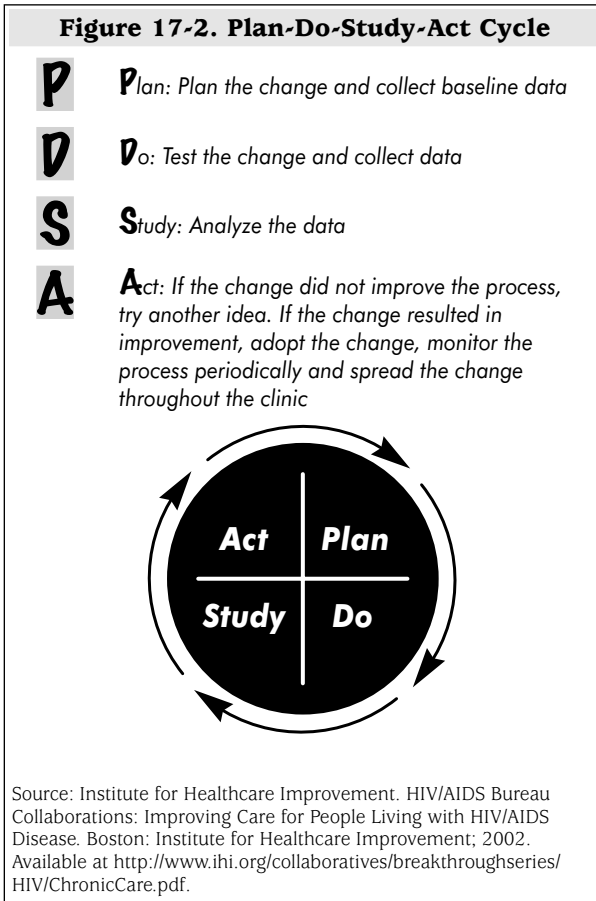


Source: *Measuring Clinical Performance: A Guide for HIV Health Care Providers*. New York, NY: New York State Department of Health AIDS Institute. April, 2002.

How does improvement occur?

Once the data have been reviewed by the team and the process for improvement identified, the next step is to decide where opportunities for improvement exist. This process is described as the PDSA (Plan-Do-Study-Act) or PDCA (Plan-Do-Check-Act) cycle (see Figure 17-2).

The first step is to investigate this care process in greater detail. Several techniques are often used to accomplish this goal. The simplest is brainstorming, in which individuals offer their suggestions for which processes are the best candidates for change. Another easy method is flowcharting, in which the group breaks down the process into its components to identify how it is coordinated and how its parts fit together. Then, the areas that would be most likely to benefit from improvement are selected for change (see Figure 17-3).



Once a change in a particular step of the process has been selected, a pilot test of the change can be quickly implemented and evaluated. A limited implementation of the proposed change can be tested – perhaps with just the next few patients, or those attending on the next day, or those seen by a particular clinician. If the pilot does not work, another change can be selected and quickly implemented. If the change is feasible and improvement is noted, then the change can be adopted more widely, before formal remeasurement occurs, and a regular period of remeasurement adopted. If the change was not successful, then another one can be chosen and tested.

What systems need to be established to support QI?

The key to sustaining QI in the clinic is development of an infrastructure that supports ongoing QI activities. The central components of this infrastructure include:

- A QI Plan with goals and a process to prioritize these goals
- An organizational framework that displays clear lines of accountability for QI in the organization

- Commitment of senior management staff to support the program, allocate resources, and celebrate its successes
- Creation of a culture that supports quality in the program and that values the activities of QI as part of the regular work of the clinic (see Table 17-5)
- Establishment of a formal QI Committee to oversee quality activities, monitor the Quality Plan, and evaluate its effectiveness

Table 17-5. Tips for Promoting a Culture of Quality Improvement: Integration of Quality into the Regular Work of the Clinic

- Educate staff about QI and provide them with the skills to participate in QI activities
- Communicate results from improvement projects throughout the clinic
- Display data and storyboards
- Celebrate successes
- Articulate the values of QI in meetings
- Provide opportunities for all staff to participate in QI teams
- Reward staff members through performance evaluation for their contributions to the QI Program

The regular, ongoing work of the QI Committee, supported by the clinic's leadership, constitutes the backbone of the infrastructure that supports ongoing QI activities. The committee oversees the dynamic process of planning, implementation, and evaluation that involves:

- Analysis of data from the QI projects
- Solicitation of feedback from participating staff
- Decision-making based on the information from its analysis

These activities contribute to sustaining the QI Program and its activities in the clinic.

Will improvements last?

Sustainability is probably the biggest challenge that clinics face in the field of QI. All too often, improvements do not last once initial projects are completed, because the structure and culture to support QI is not present or is not supported. The challenge of sustainability is therefore two-fold – not only to maintain the successes of QI work and its clinical outcomes, but also to maintain the systems of QI and to keep the QI program vital. By asking questions about how care systems can be improved and how QI activities are progressing, clinicians play an important role in both catalyzing and supporting QI activities.

What are the key components of a quality plan?

The key elements of a quality plan include a quality statement that describes the purpose and goals of the QI program, priorities of the program, a description of the organizational systems needed to implement the program, including committee structure and functions, definitions of accountability, roles and responsibilities, the process for obtaining consumer input, core measures, data collection processes, and a description of how the plan will be evaluated.

KEY POINTS

Providers play an active role in the activities of QI and can lead these efforts by asking questions to determine how improvements can be made. Although the QI program may require extra work from busy providers, the opportunities to systematically measure clinical performance will provide useful information that leads to better care for the patients they serve.

QI includes regular measurement of care processes, analysis of processes and systems of care, and implementation of solutions to improve care and monitor their effectiveness. The goal of QI is to achieve optimal health outcomes for patients.

QI teams identify areas of change, implement pilots to test the change, review data assessing the change, and ultimately make recommendations about improvements. When staff members from the systems being assessed work together in teams and are engaged in the QI process, they are more likely to generate ideas and to accept changes.

Indicators, measurable aspects of care that evaluate the extent to which a facility provides a certain element of care, should be based on standards or guidelines, meet the primary goals of QI, and reflect priorities specific to the community and the clinic.

Once data have been reviewed by the team and the process for improvement identified, the next step is to decide where opportunities for improvement exist. This process is described as the PDSA (Plan-Do-Study-Act) process. The first step is to investigate this care process in greater detail. Once a change in a particular step of the process has been selected, a pilot test of the change can be quickly implemented and evaluated. If the pilot is successful, the change can be adopted widely. If the pilot is not successful, another change can be selected and tested.

Sustainability is probably the biggest challenge that clinics face in the field of QI. The key to sustaining QI in the clinic is development of an infrastructure that supports ongoing QI activities.



SUGGESTED RESOURCES

AETC National Resource Center and New York State Department of Health AIDS Institute. *Measuring Clinical Performance: A Guide for HIV Healthcare Providers*. Available at http://www.hivguidelines.org/public_html/center/quality-of-care/perform_guide/perform-guide-intro.htm Accessed 1/04.

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McGlynn EA, Asch SM. *Developing a Clinical Performance Measure*. *Am J Prev Med*. 1998;14(3 Suppl):14-21.

New York State Department of Health AIDS Institute. *HIVQUAL Group Learning Guide: Interactive Quality Improvement Exercises for HIV Healthcare Providers*. http://www.hivguidelines.org/public_html/center/quality-of-care/performance_measurement_materials/glg/group_learning_guide.

Scholtes PR, Joiner BL, Streibel BJ. *The Team Handbook* (3rd Ed). Madison: Oriol, Inc; 2003.



WEBSITES*

HIV-Specific Examples

<http://hab.hrsa.gov/special/qualitycare.htm>

<http://hab.hrsa.gov/tools/QM>

<http://www.hivguidelines.org>
Quality of Care Section.

<http://www.qualityhealthcare.org/QHC/Topics/HIVAIDS>

<http://www.ihl.org/collaboratives/breakthroughseries/hiv>

<http://www.qaproject.org>

General QI Websites

<http://www.qualityhealthcare.org/qhc>

<http://www.ihl.org>
(Institute for Healthcare Improvement)

<http://www.isqua.org.au> (International Society for Quality in Health Care)

<http://www.asq.org>
(American Society for Quality)

<http://www.mytapestry.com>
(contains many links to other websites)

<http://www.ahrq.gov> (Agency for Healthcare Research and Quality)

<http://www.jcaho.org> (Joint Commission on Accreditation of Healthcare Organizations)

<http://www.nahq.org>
(National Association of Healthcare Quality)

http://www.musc.edu/fm_ruralclerkship/
(Family Medicine/Rural Clerkship CQI)

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