



Comorbidities, Coinfections, and Complications in HIV Patients



Introduction

HIV/AIDS clinical care has improved dramatically over the decades, given the availability of new medications and a better understanding of how best to use antiretrovirals and deliver primary care to persons living with HIV/AIDS. Positive change on such a massive scale, however, brings with it new demands on clinicians.

Along with innovations in HIV drug therapies, HIV/AIDS care has become more complex than ever before due to increasing comorbidities that are attributable to HIV treatment and the aging of the HIV-infected population in the United States. Patient needs also have expanded across a broad spectrum of medical, psychological, behavioral, and social issues. Notably, significant numbers of infected individuals are identified and enter care late in the course of their HIV disease, confronting clinicians with complex and immediate care challenges.

Since the early days of the epidemic, clinicians have received training in HIV/AIDS clinical care through the AIDS Education and Training Centers (AETCs) Program – the clinical training arm of the Ryan White HIV/AIDS Program that is administered by the Health Resources and Services Administration (HRSA) and its HIV/AIDS Bureau (HAB). The AETC network conducts more than 14,000 training events each year with approximately 143,000 health care providers in attendance.

The *Guide for HIV/AIDS Clinical Care* is a pillar of the Ryan White HIV/AIDS Program's mission to continuously improve HIV/AIDS clinical care. The *Guide* was first published in 1993 as a collaborative effort of several regional AETCs. It was subsequently updated and expanded in 2006 and 2011. The version before you incorporates many new insights, but the time-tested format has been retained – easy access to crucial facts for a busy clinician.

The developers of the *Guide* strive to be responsive to how HIV/AIDS clinical care is provided today.

- With more routine HIV testing in medical settings, a large number of individuals are entering care via primary care sites that have relatively limited experience managing HIV/AIDS disease.
- A notable proportion of HIV/AIDS primary care in the United States is provided by advanced practice nurses and physician assistants.
- Shortages in the health care work force are worsening. Experienced staff members are aging and retiring, a limited number of new clinicians are entering primary care and specializing in HIV/AIDS care, and fewer clinicians are available in geographic areas with limited resources.

As a result, front line primary care providers may be less familiar with management of HIV/AIDS disease, as outlined in U.S. Department of Health and Human Services treatment guidelines (available at aidsinfo.nih.gov) and clinical practices presented in this *Guide*.

By presenting best practices in the clinical management of HIV/AIDS disease, the *Guide* can help us continue the remarkable advances in HIV/AIDS care that have made the Ryan White HIV/AIDS Program a model for health care delivery for our Nation and for the world.

Abbreviations for Dosing Terminology

BID = twice daily

BIW = twice weekly

IM = intramuscular (injection), intramuscularly

IV = intravenous (injection), intravenously

PO = oral, orally

Q2H, Q4H, etc. = every 2 hours, every 4 hours, etc.

QAM = every morning

QH = every hour

QHS = every night at bedtime

QID = four times daily

QOD = every other day

QPM = every evening

TID = three times daily

TIW = three times weekly



Abnormalities of Body-Fat Distribution

Background

Abnormalities of body-fat distribution are a recognized complication of HIV infection and of antiretroviral therapy (ART), and they are a common concern of patients. They include central fat accumulation (lipohypertrophy) and subcutaneous fat wasting (lipoatrophy). These morphologic changes are often referred to as lipodystrophy, though that term fails to distinguish between the two phenomena. Abnormalities in fat distribution and body shape have been noted in up to 40-50% of patients treated with older antiretroviral (ARV) medications, but the incidence may be much lower with the use of newer, less lipotoxic ARVs and with earlier initiation of ART. Lipohypertrophy and lipoatrophy are associated with other metabolic abnormalities, such as dyslipidemia and insulin resistance, and visceral fat accumulation (at least in HIV-uninfected persons) is a risk factor for cardiovascular disease.

Research on fat maldistribution has yielded varying results, in part because there are no standard clinical case definitions of lipodystrophy, lipoatrophy, or lipohypertrophy. The pathogenesis of fat abnormalities in HIV-infected individuals is not well understood, but research to date suggests that it is multifactorial and is associated with HIV-related immune depletion and immune recovery, ARV medications, dysregulation of fatty acid metabolism, hormonal influences, individual genetic predispositions, and factors that are not related to HIV such as diet and obesity. Lipodystrophy has been associated with lower nadir CD4 count as well as with gender (central lipohypertrophy may be more common in women) and age (more common in older patients), and longer exposure to ART. Lipohypertrophy has not been definitively proven to be related to specific ARVs or to specific ARV classes, but has been variably associated with protease inhibitors (PIs) and with nucleoside reverse transcriptase inhibitors (NRTIs). However, morphologic changes occasionally develop in ARV-naïve individuals. Lipoatrophy is most commonly associated with NRTIs, notably stavudine, as well as didanosine and zidovudine.

The most common morphologic changes seen in lipohypertrophy are a firm enlarged abdomen caused by central or visceral fat accumulation, breast enlargement (gynecomastia) in both men and women, development of a dorsocervical fat pad ("buffalo hump"), and neck enlargement. Lipoatrophy most commonly appears as the loss of subcutaneous fat in the face, arms, legs, and buttocks. Lipoatrophy differs from the generalized wasting seen in advanced AIDS, because lean cell mass generally is preserved. When lipohypertrophy and lipoatrophy occur together, the affected individuals show a mixed picture of abdominal obesity with thinning in the face, arms, and legs.

Severe lipoaccumulation can cause discomfort and, in some cases, impairment of breathing or other bodily functions. It may be associated with other metabolic abnormalities, including dyslipidemia, insulin resistance, and the metabolic syndrome. Both lipoaccumulation and lipoatrophy can be disfiguring, can damage self-image and quality of life, and can negatively influence ARV adherence.

S: Subjective

The patient may report any of the following: abdominal fat accumulation with change in waist size, increased neck size, “buffalo hump,” enlarged breasts, and reduced range of motion. Alternatively (or in addition), the patient may report sunken cheeks, decreased arm or leg circumference, prominence of veins in the arms or legs, or buttock flattening.

Determine CD4 cell count nadir, ARV medication history with particular attention to past use of thymidine analogues and PIs, and duration of and response to each regimen. Ask about past medical and family history, specifically regarding hyperlipidemia, diabetes or insulin resistance, other metabolic disorders, and cardiovascular disease. Evaluate the effect of body-shape changes on the patient’s self-esteem, medication adherence, and interpersonal relationships.

O: Objective

Compare past and current weights. Calculate body mass index (BMI); see chapter *Initial Physical Examination* for information on BMI.

Measure and document waist and hip circumferences. A waist circumference of >102 cm (39 inches) in men and >88 cm (35 inches) in women is the clinical definition of abdominal obesity and is associated with the metabolic syndrome. Waist-to-hip ratios of >0.95 in men and >0.85 in women have been associated with an increased risk of coronary heart disease.

Examine the head, neck, back, breasts, and abdomen for fat accumulation, especially looking for dorsocervical fat pad and facial, neck, or breast enlargement. Examine the face and extremities for subcutaneous fat loss (e.g., in the cheeks, temples, limbs, and buttocks).

Review laboratory history (glucose, lipid panel) to identify other metabolic disorders. (See chapters *Dyslipidemia* and *Insulin Resistance, Hyperglycemia, and Diabetes on Antiretroviral Therapy*.)

A: Assessment

No uniform standard criteria are available for defining or grading lipohypertrophy or lipoatrophy in clinical practice. Clinicians must base their assessment on patient self-report, physical examination (for characteristic body-shape changes), associated symptoms, and psychological consequences.

In research settings, modalities such as dual-energy X-ray absorptiometry (DEXA), computed tomography (CT), and magnetic resonance imaging (MRI) have been used to characterize and quantify lipoaccumulation and lipoatrophy. Anthropometric measurements may be made in the clinic by trained personnel (e.g., nutritionists), but do not measure visceral fat directly. Although measurements such as waist circumference cannot be used to assess lipohypertrophy, they have been validated (in HIV-uninfected individuals) as an assessment of cardiovascular risk (see chapters *Dyslipidemia* and *Coronary Heart Disease Risk*). Bioelectrical impedance analysis (BIA) does not measure regional body composition and thus is not used to measure abnormal body-fat changes.

Differential diagnosis of lipohypertrophy includes obesity or excess weight gain, ascites, and Cushing syndrome.

Differential diagnosis of lipoatrophy includes weight loss and wasting.

P: Plan

Diagnostic Evaluation

Laboratory

Check for other metabolic abnormalities associated with the use of ARVs, such as dyslipidemia and impaired glucose metabolism (check fasting lipids and random or fasting glucose). See chapters *Dyslipidemia* and *Insulin Resistance, Hyperglycemia, and Diabetes on Antiretroviral Therapy* for further information about workup and treatment.

Treatment

Treatments for lipohypertrophy and lipoatrophy have not reliably reversed body shape changes once these changes have occurred. In general, treatment interventions have shown poor results in patients with marked or severe fat maldistribution and inconsistent or limited responses in those with milder conditions. The best approaches to managing lipodystrophy are prevention and early intervention.

Clinicians can help to prevent body fat abnormalities by avoiding, whenever possible, ARV agents known to confer a greater risk of this disorder (particularly stavudine, didanosine, and zidovudine, which are most closely associated with lipoatrophy). All patients who take ARVs should be monitored carefully for the development of fat maldistribution. If abnormalities are noticed, the suspect ARV should be discontinued and a more benign ARV started in its place, if possible.

The optimal management strategy for established lipoaccumulation or lipoatrophy is not known, although the following approaches can be considered (see below). Also consider referring the patient to clinical studies of lipodystrophy treatment, and for psychological or adherence support and counseling, if indicated. If the patient is distressed enough to consider discontinuing or interrupting ART, review with the patient any gains he or she has made on ART and discuss treatment options (see below). In some cases the patient may insist on discontinuing ARV medications; in this situation, carefully review the risks of treatment interruption as well as the alternatives to discontinuing treatment.

ARV Substitutions

Avoiding thymidine analogue NRTIs, particularly stavudine, and avoiding the NRTI combination stavudine + didanosine have been shown to reduce the risk of lipoatrophy.

In patients with lipoatrophy, modest slow improvement in limb fat has been demonstrated after switching from thymidine analogues (stavudine, zidovudine) to nonthymidine NRTIs (such as abacavir or tenofovir) or to NRTI-sparing regimens. In patients with lipohypertrophy, similar NRTI switch strategies have had little effect on visceral or trunk fat. Studies in which PIs were eliminated from the ART regimen generally have not shown significant effects on body fat measures.

Before switching therapies, carefully assess the potential risk to the patient's long-term HIV management.

Nonpharmacologic Measures

Diet

The effects of diet on lipohypertrophy have not been evaluated thoroughly. If overall weight reduction is needed, recommend dietary changes and exercise. Avoid rapid weight loss plans, as lean body mass often is lost disproportionately. Refer to a dietitian to help the patient decrease intake of saturated fat, simple sugars, and alcohol.

Exercise

Regular, vigorous cardiovascular exercise may help control central fat accumulation, whereas resistance exercises (strength training) will improve the ratio of muscle to fat. Some studies of exercise (done alone or in combination with diet) have shown a reduction in visceral fat accumulation with minimal or no changes in peripheral lipoatrophy. Moderate aerobic exercise should be encouraged for all patients.

Pharmacologic Measures

Insulin-sensitizing agents

In diabetic and non-HIV lipodystrophy, treatment with thiazolidinediones may decrease visceral fat, increase peripheral fat, and improve glycemic control. In HIV-infected patients with lipoatrophy, studies of thiazolidinediones, specifically rosiglitazone and pioglitazone, have shown mixed results. Some patients have reported improvement in limb fat, particularly those with insulin resistance; however, a larger, 48-week randomized trial of rosiglitazone found no significant increase in limb-fat mass. In patients with visceral fat accumulation, thiazolidinediones have not been found to be effective.

In clinical studies, metformin has been modestly effective in treating visceral adiposity in patients with insulin resistance, but may cause worsening of lipoatrophy. Metformin should be used with caution in patients with chronic liver or renal disease.

Growth hormone-releasing factor

Tesamorelin, a synthetic growth hormone-releasing factor analogue, is approved by the U.S. Food and Drug Administration (FDA) for treatment of excess abdominal fat in HIV-infected persons with lipodystrophy. It has been shown to reduce central fat accumulation by about 18% over the course of 12 months, without adverse effects on glucose or lipid parameters. Unfortunately, patients rapidly regain visceral fat when tesamorelin is discontinued. That, along with its expense, has limited the use of tesamorelin. No long-term safety data are available.

Recombinant human growth hormone

Treatment with recombinant human growth hormone (rHGH), 3-6 mg/day for 12 weeks followed by maintenance therapy with lower doses of 1-2 mg/day, has been shown to reduce visceral fat in many patients with minimal impact on peripheral fat wasting; other studies suggest efficacy (and improved tolerability) of lower dosages of rHGH. However, the high cost of rHGH, the high rate of adverse effects (including insulin resistance), and the frequent recurrence of visceral fat accumulation once rHGH is discontinued have resulted in a limited role for this treatment.

Plastic and reconstructive surgery

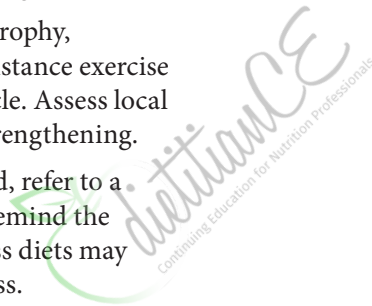
Various techniques have been investigated, but generally have limited applicability and efficacy. Poly-L-lactic acid (Sculptra, New-Fill) and a calcium hydroxylapatite preparation (Radiesse) are approved by the FDA as treatments for facial lipoatrophy. These injectable materials have shown good cosmetic results and often significantly improve patients' satisfaction with their appearance. Treatment effects of both agents typically wane with time and the procedures often must be repeated. Other facial fillers, as well as cheek implants and autologous fat transfer, have been used successfully in some cases. For lipoaccumulation, treatments such as liposuction for focal areas of fat deposition

(e.g., dorsocervical) and breast reduction may be effective in the short term, though fat often reaccumulates.

These interventions may be covered by private- and public-payer sources, but still often are deemed to be the financial responsibility of the patient. In some cases, they may be only a temporary solution, because abnormalities may reappear after treatment.

Patient Education

- Instruct patients who are receiving ARV medications to inform their health care provider if they notice changes in the shape or appearance of their bodies.
- Review the importance and benefits of ART and assess adherence to the regimen.
- For patients with lipohypertrophy, recommend aerobic and resistance exercise to reduce fat and build muscle. Assess local resources for safe muscle-strengthening.
- If weight reduction is needed, refer to a dietitian for consultation. Remind the patient that quick weight-loss diets may result in excessive muscle loss.
- For patients with severe facial lipoatrophy, consider referral to an experienced dermatologist or plastic surgeon for restorative treatment.



Dyslipidemia

Background

HIV-infected individuals, both those on antiretroviral therapy (ART) and those who are untreated, appear to have higher rates of coronary heart disease (CHD) than HIV-uninfected individuals and higher rates of various risk factors for CHD, including dyslipidemia. As the average lifespan of patients on effective ART lengthens, and as people living with HIV become older, morbidity and mortality from CHD are likely to continue to increase. Thus, identification and reduction of modifiable risk factors for CHD are important aspects of primary care for HIV-infected patients.

Dyslipidemia is a well-described independent risk factor for CHD, and it occurs in a high proportion of persons with HIV infection. Current research suggests that this dyslipidemia is caused by a combination of factors related to HIV disease, ART regimens, and individual patient characteristics. HIV itself causes lipid perturbations, particularly in persons with more advanced immunosuppression; HIV-infected individuals who are not on antiretroviral (ARV) medications often have elevations in triglyceride (TG) levels and decreases in high-density lipoprotein (HDL) as well as in low-density lipoprotein (LDL) cholesterol and total cholesterol (TC). Lipid abnormalities also may be caused by or compounded by ARVs (see chapter *Coronary Heart Disease Risk*). They may appear or worsen within a few weeks to months after starting ART. With some patients, this may, at least in part, represent a return to pre-illness lipid levels, whereas the ARVs cause the abnormality in other cases.

Not all ART-treated patients experience lipid abnormalities to the same degree. Patients with a personal or family history of dyslipidemia, glucose intolerance, diabetes, obesity, or a combination of these health problems may be genetically predisposed to lipid abnormalities that become evident once ART is initiated.

The use of potent combination ART, particularly the use of protease inhibitors (PIs), has increased the prevalence of abnormally high TG, TC, and LDL levels among HIV-infected patients. In fact, dyslipidemia has been associated not only with certain PIs but also with certain nonnucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs). In the PI class, ritonavir-boosted PIs (though unusually with atazanavir or darunavir) are particularly likely to cause marked elevations of TG and LDL levels. Although NNRTIs also may contribute to increases in TC, LDL, and TG levels the effects, particularly with efavirenz, are more variable (and efavirenz may increase HDL). Of the NRTIs, stavudine, zidovudine, and perhaps abacavir may increase TC and TG levels. To date, available agents from the integrase inhibitor and CCR5 antagonist classes do not appear to have significant adverse impacts on lipid levels.

The largest prospective study of CHD events related to ARVs (the D:A:D study) showed a small but significant increase in the risk of myocardial infarction among HIV-infected patients treated with ARVs; moreover, the effect increased with cumulative years of ARV exposure. This effect was largely but not entirely associated with increases in LDL cholesterol (see chapter *Coronary Heart Disease Risk*).

HRSA HAB Performance Measures

Percentage of patients, regardless of age, with a diagnosis of HIV who were prescribed HIV antiretroviral therapy and who had a **fasting lipid panel** during the measurement year

(All-Age measure)

Identification and management of dyslipidemia in HIV-infected patients is an important part of HIV primary care. For patients with CHD or CHD risk equivalents (see below), ART regimens should, if possible, be selected to minimize the risk of hyperlipidemia.

Guidelines for the evaluation and management of dyslipidemia have been developed by the National Cholesterol Education Program (NCEP). These recommendations are based on studies of HIV-uninfected persons and may not be entirely applicable to HIV-infected persons, in whom HIV itself may increase risk of CHD events. Despite this limitation, expert panels generally recommend similar treatment goals when evaluating and managing dyslipidemia in patients with HIV infection. (For recommendations on screening, see chapter *Initial and Interim Laboratory and Other Tests*.)

Note: The American College of Cardiology and the American Heart Association released new guidelines on treatment of hyperlipidemia late in 2013. These take a different approach to many aspects of lipid management, including the evaluation of patients for lipid-lowering therapy, the use and monitoring of lipid lowering agents, and the use of treatment targets. These guidelines have generated controversy. As their appropriateness to the management of HIV-infected individuals is not clear at this time, this chapter will discuss the approach presented in the NCEP guidelines.

S: Subjective

The history should focus on factors that suggest CHD, risk equivalents, or risk factors for CHD. Both CHD risks and CHD equivalents should be the focus of lifestyle modification strategies and lipid-normalizing treatment.

- **CHD** includes the following:
 - A history of myocardial infarction
 - Angina
 - CHD procedures
 - Evidence of clinically significant myocardial ischemia
- **CHD risk equivalents** are considered to be equal in terms of risk level to known CHD. These include the following:
 - Diabetes mellitus
 - Peripheral vascular disease
 - Symptomatic carotid artery disease
 - Abdominal aortic aneurysm
 - Transient ischemic attacks
 - Two or more CHD risk factors with a 10-year risk of CHD >20% (see “Calculations to Estimate the 10-Year Risk of Cardiac Events for Men and Women,” below, or the online risk calculator at cvdrisk.nhlbi.nih.gov/calculator.asp).

- **CHD risk factors** are conditions associated with a greater risk of serious cardiac events. These are as follows:

- Male sex
- Age (≥ 45 in men; ≥ 55 in women)
- Hypertension
- Cigarette smoking
- Low HDL (< 40 mg/dL); if > 60 mg/dL, subtract one risk factor
- Family history of premature CHD (first-degree relative aged < 55 [men] or < 65 [women])
- Assess for causes of secondary dyslipidemias, including insulin resistance, diabetes, hypothyroidism, obstructive liver diseases, chronic renal failure, and medications such as corticosteroids and progestins.
- Screen for other factors that contribute to hyperlipidemia, including obesity, chronic liver diseases, alcohol abuse, high-fat or high-carbohydrate diet, and prothrombotic or proinflammatory states.
- Screen for health behaviors that increase CHD risk, including smoking, high-fat diet, sedentary lifestyle, and use of recreational drugs such as cocaine and methamphetamine.

- Review the patient's family history for premature CHD (as discussed above), obesity (body mass index [BMI] ≥ 30), diabetes, and lipid abnormalities.
- Review the patient's medications, with special attention to ARVs known to increase LDL or TG levels (particularly ritonavir and ritonavir-boosted PIs).

O: Objective

Check vital signs with special attention to blood pressure and weight. Calculate BMI (see chapter *Initial Physical Examination* for information on BMI).

Perform a focused physical examination with particular attention to signs of hyperlipidemia, such as xanthelasma and xanthoma, and to the cardiovascular system.

A: Assessment

Determine whether a specific intervention is appropriate based on the patient's lipid values and identified CHD risks, as indicated in Tables 1 and 2.

LDL is the main indicator for treatment, and the main target for lipid-lowering therapy. Hypertriglyceridemia is associated with CHD risk, but thresholds of risk have not been defined precisely, and targets for intervention are not entirely clear (for persons with triglyceride levels of ≥ 500 mg/dL, the triglycerides usually are treated first; see "Treatment," below). Severe hypertriglyceridemia (e.g., TG $>1,000$ mg/dL) also increases the risk of pancreatitis.

For patients who do not have diabetes or preexisting CHD and who have two or more CHD risk factors, calculate the "10-year risk of cardiovascular events" by using the Risk Assessment Tool for estimating the 10-year risk of a major CHD event. Use the risk-estimate tool at the end of this chapter or the online risk calculator at the National Institutes of Health website (cvdrisk.nhlbi.nih.gov/calculator.asp).

Table 1. Low-Density Lipoprotein Cholesterol Goals and Thresholds for Treatment*

Risk Category	LDL Goal*	Initiate Therapeutic Lifestyle Changes	Consider Drug Therapy
Lower risk: No CHD or CHD risk equivalents and <0 -1 risk factor	<160 mg/dL (<4.1 mmol/L)	LDL ≥ 160 mg/dL (≥ 4.1 mmol/L)	≥ 190 mg/dL (≥ 4.9 mmol/L); at 160-189 mg/dL, LDL drug therapy is optional
Moderate risk: No CHD or CHD risk equivalents and ≥ 2 risk factors, with 10-year estimated risk $<10\%$	<130 mg/dL (<3.4 mmol/L)	LDL ≥ 130 mg/dL (≥ 3.4 mmol/L)	≥ 160 mg/dL (≥ 4.1 mmol/L)
Moderately high risk: No CHD or CHD risk equivalents and ≥ 2 risk factors and 10-year estimated risk 10-20%	<130 mg/dL (<3.4 mmol/L) (optional goal of <100 mg/dL)	LDL ≥ 130 mg/dL (≥ 3.4 mmol/L)	≥ 130 mg/dL (≥ 3.4 mmol/L)
High risk: CHD or CHD risk equivalent (see above)	<100 mg/dL (<2.6 mmol/L) (optional goal of <70 mg/dL#)	LDL ≥ 100 mg/dL (≥ 2.6 mmol/L)	≥ 100 mg/dL (≥ 2.6 mmol/L)

Table 2. Classification of Triglyceride Levels

Risk Category	Triglyceride Measurement	Initiate therapy
Normal triglycerides	<150 mg/dL	
Borderline-high triglycerides	150-199 mg/dL	
High triglycerides	200-499 mg/dL	Start therapeutic lifestyle changes; consider medication if CHD, CHD equivalents, or high risk
Very high triglycerides	≥500 mg/dL	Start therapeutic lifestyle changes; consider medication

P: Plan

Diagnostic Evaluation

The fasting serum lipid panel should be performed at least 8 hours, but ideally 12 hours, after last food and beverage intake. It measures TC, HDL, TG, non-HDL cholesterol with calculated LDL, and TC/HDL cholesterol ratio.

A fasting lipid panel should be checked at baseline, before patients start ART.

Repeat the fasting lipid panel within 3-6 months after ARVs are started, and sooner for patients who have abnormal values at baseline.

Patients with normal lipid values should be rechecked annually (sooner if ARVs are changed). Those with dyslipidemia may need more intensive monitoring (e.g., every 4-6 weeks) until the LDL goal is met, after which monitoring every 4-6 months is adequate.

Treatment

Treatment of dyslipidemia usually involves a multimodal approach, including diet and exercise in all cases, lipid-modifying medication, and consideration of changes in ARV medication. The primary goal of lipid-lowering therapy is to reduce LDL to target levels. For persons with CHD and CHD risk equivalents, the type and intensity of LDL lowering therapies are adjusted according to LDL baseline levels. Note that other interventions to reduce CHD risk also should be undertaken (e.g., smoking cessation if appropriate).

For patients with serum TG level of >400 mg/dL, the LDL cholesterol calculation is unreliable. In this situation, non-HDL cholesterol (TC minus HDL) can be used as a surrogate target of therapy; the non-HDL goal is 30 mg/dL higher than the LDL goal. For these individuals, dietary intervention is warranted, and drug therapy to decrease LDL (or non-HDL) can be considered if TC is >240 mg/dL or HDL cholesterol is <35 mg/dL. For those with TG levels of 200-500 mg/dL, achieving the LDL cholesterol target is the primary goal, and lowering non-HDL cholesterol levels is a secondary goal (see Table 1 for LDL intervention levels).

The NCEP guidelines recommend that very high TG levels (≥500 mg/dL) be reduced before LDL is treated directly (see “Treatment of hypertriglyceridemia,” below).

The LDL levels at which either therapeutic lifestyle change (TLC) or drug therapy should be initiated are shown in Table 1, along with the target goals for LDL cholesterol. The response to therapy should be monitored and therapeutic interventions should be intensified or augmented until lipid targets are met.

Therapeutic lifestyle change

TLC, consisting of diet modification and exercise, is fundamental to the management of dyslipidemia for HIV-infected patients.

Target goals for lipid abnormalities are difficult to achieve without prioritizing these behavioral change efforts. Although TLC is hard to maintain, it can yield significant results in reducing CHD risk and improving quality of life. Effective TLC is best achieved with a multidisciplinary team approach. HIV primary care providers should be instrumental in identifying TLC as a treatment priority and providing referrals to nutritionists for dietary counseling, to mental health professionals for assessment of treatable mood disorders, and to social workers, peer counselors, or clinical nurse specialists for assistance with health-behavior changes, self-care strategies, and identification of resources in the community for smoking cessation support and exercise programs. Specific recommendations for TLC goals and behavior change strategies are contained in the Adult Treatment Panel guidelines, which are available at www.nhlbi.nih.gov/guidelines/cholesterol/index.htm.

Pharmacologic treatment for hypercholesterolemia

All patients with elevated lipid levels should initiate TLC. If pharmacologic intervention is indicated, statins (hydroxymethylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are the first-line treatment for most patients. These agents can be effective in reducing TC, LDL, and non-HDL cholesterol levels

in HIV-infected patients (see Table 3). More importantly, they have been shown to reduce the risk of cardiovascular events in persons with or at risk of CHD.

Recommended starting dosages of statins for patients taking PIs are as follows (Note: see “Potential ARV Interactions,” below):

- Pravastatin: 20 mg PO QD
- Atorvastatin: 10 mg PO QD

Fibrates may be considered as an alternative or adjunct to statins (see “Treatment of hypertriglyceridemia,” below, for further information). When given concomitantly, statins and fibrates increase the risk of rhabdomyolysis and must be used cautiously and with careful monitoring). Niacin may be effective as adjunctive therapy, but it has not been shown to decrease CHD events. It may worsen insulin resistance and may cause hepatotoxicity. It also causes uncomfortable flushing in some patients; the sustained-release formulations are better tolerated. Ezetimibe (Zetia) appears to be effective in combination with statins for patients whose cholesterol is not controlled adequately with a statin alone, but it also has not been shown to decrease CHD events. Bile acid sequestrants generally should be avoided because they may interfere with the absorption of other drugs and may increase TG levels.

Table 3. Drug Treatments for Lipid Abnormalities

Lipid Abnormality	First Choice	Second Choice	Comments
Isolated high LDL, non-HDL cholesterol	Statin	Fibrate	Start with pravastatin* or atorvastatin* (available as generics). Use low statin dosages and titrate upward; patients taking PIs have increased risk of myopathy.
Isolated high TG	Fibrate	Statin, N-3 (omega-3) fatty acids	Start with gemfibrozil or fenofibrate. Combined statin and fibrate may increase myopathy risk.
High LDL and TG (TG level 200-500 mg/dL)	Statin	Fibrate	Start with pravastatin or atorvastatin* (available as generics). Use fluvastatin,* rosuvastatin,* pitavastatin,* gemfibrozil, or fenofibrate as alternatives. Combined statin and fibrate may increase myopathy risk.
High LDL and TG (TG level >500 mg/dL)	Fibrate	N-3 (omega-3) fatty acids, niacin, statin	Start with gemfibrozil or fenofibrate. Niacin is associated with insulin resistance. May need to add statin if cholesterol is not controlled adequately.

Potential ARV Interactions

Clinicians should note that there are clinically significant drug interactions between most statins and PIs, NNRTIs, and the pharmacokinetic enhancer cobicistat (see Table 4). PIs and cobicistat can increase serum levels of most statins significantly, thus increasing the risk of severe statin adverse events such as rhabdomyolysis. Of the statin drugs, pravastatin is the least affected by most PIs (darunavir is an exception) and is the recommended statin for most patients with hypercholesterolemia without hypertriglyceridemia. Atorvastatin, if used, should be initiated at low dosage (10 mg) and titrated slowly upward to achieve target lipid levels (note that atorvastatin may lower TG, TC, and LDL levels). Lovastatin and simvastatin are contraindicated for use by patients taking PIs or cobicistat. These can result in severe statin-related adverse events if prescribed. Other available statins include rosuvastatin, pitavastatin, and fluvastatin. These have not been as well studied but may be used with most PIs (there are exceptions; see table on the following page). When statins are given concurrently with interacting PIs, the statins should be started at low dosage and increased incrementally, if indicated; in general, maximum dosages should not be used.

NNRTIs decrease levels of most statins (however, etravirine increases fluvastatin levels); higher dosages of statins may be needed to overcome this interaction. Be aware that various formulations and combination products contain these statins; check the generic name of components in new or unfamiliar cardiac prescriptions to determine whether they contain lipid-lowering agents.

The integrase inhibitors dolutegravir and raltegravir, and other classes of ARV drugs (NRTI, fusion inhibitor, CCR5 antagonist), do not have recognized interactions with statins. Other types of lipid-lowering medications generally are not metabolized by hepatic cytochrome P450 and are not affected by ARVs (an exception to this is gemfibrozil, whose levels are decreased by lopinavir/ritonavir, by an unknown mechanism).



Table 4. Interactions Between Statin Agents and Antiretroviral Medications

Code:

✓ Generally safe to begin treatment with usual starting dosage

! Caution; start with low dosage, monitor effects



Contraindication is contraindicated

	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin*	Simvastatin
Protease Inhibitors							
Atazanavir	!	No data	☒	✓(unboosted) ! (ritonavir boosted)	!	! Rosuvastatin AUC ↑ 213%; C _{max} ↑ 600%	☒
Darunavir/ritonavir	!	No data	☒	✓	! Pravastatin AUC ↑ 81% to 500%	!	☒
Fosamprenavir	!	No data	☒	No data	✓May need to ↑ pravastatin dosage	✓	☒
Indinavir	!	No data	☒	☒	!	!	☒
Lopinavir/ritonavir	! Atorvastatin AUC ↑ 488%	No data	☒	✓	✓pravastatin AUC ↑ 33%	! Rosuvastatin AUC ↑ 108%; C _{max} ↑ 466%	☒
Nelfinavir	!	No data	☒	No data	!	No data	☒
Ritonavir	!	No data	☒	No data	!	No data	☒
Saquinavir	!	No data	☒	No data	✓saquinavir + ritonavir: May need to ↑ pravastatin dosage	No data	☒
Tipranavir	☒ Atorvastatin AUC ↑ 836%	No data	☒	No data	!	✓Rosuvast AUC ↑ 26%	☒
Nonnucleoside Reverse Transcriptase Inhibitors							
Efavirenz ^A	✓May need to ↑ atorvastatin dosage	No data	✓May need to ↑ lovastatin dosage	No data	✓May need to ↑ pravastatin dosage	No data	✓May need to ↑ simvastatin dosage
Etravirine	✓May need to ↑ atorvastatin dosage	No data; May ↑ fluvastatin levels	✓May need to ↑ lovastatin dosage	No data	✓	No data	✓May need to ↑ simvastatin dosage
Rilpivirine	✓	No data	No data	No data	No data	No data	No data
Integrase Inhibitor/Cobicistat Combination							
Elvitegravir/cobicistat	!	No data	☒	No data	No data	✓Rosuvast AUC ↑ 38%	☒

Treatment of hypertriglyceridemia

Patients with TG levels of 200-500 mg/dL should begin non-drug interventions such as diet modification, reduction in alcohol consumption, aerobic exercise, and smoking cessation. When the TG level is ≥ 500 mg/dL, a low-fat diet ($<15\%$ of caloric intake) is recommended to help prevent pancreatitis, and pharmacologic therapy probably will be required. Patients with CHD or CHD equivalents, those at high risk of CHD, and those with TG levels >200 mg/dL may need pharmacologic therapy.

Fibrates are the first-line drug option for isolated hypertriglyceridemia and are an alternative treatment for combined hypertriglyceridemia and hypercholesterolemia. Fenofibrate or gemfibrozil reduce TG levels effectively in patients on ARVs. Because they are not metabolized by the cytochrome P450 hepatic enzyme system, they do not have significant drug interactions with most ARVs (an exception may be gemfibrozil with dolutegravir: dolutegravir levels may be increased). Fibrates are contraindicated for use by patients with renal failure. Recommended dosages of these agents are as follows:

- Fenofibrate: 40-200 mg PO QD
- Gemfibrozil: 600 mg PO BID, 30 minutes before meals

If a fibrate alone is inadequate in reducing TG levels, several options are possible. A statin (e.g., atorvastatin, which acts on TGs as well as cholesterol) could be added cautiously, although there is an increased risk of skeletal muscle toxicity with concomitant use of a fibrate and a statin. N-3 (omega-3) fatty acid supplements (e.g., fish oils), administered at 1-2 g BID or TID, have decreased TG levels in patients taking ART. Extended-release niacin at 1,500-2,000 mg/day also decreases both TG and TC levels, although its clinical utility is restricted because of associated insulin resistance and flushing.

Switching antiretroviral therapy

For patients with CHD or CHD equivalents, ARV medications should, if possible, be selected to minimize the risk of hyperlipidemia. In patients with dyslipidemia caused by ARV agents, data suggest that it may be beneficial to discontinue ARVs known to increase lipids if reasonable alternatives exist. Substituting atazanavir or an integrase inhibitor in place of a lipogenic PI or replacing stavudine with tenofovir may improve the lipid profile. Before making ARV substitutions, however, consider carefully the possible effect of the substitution on HIV virologic control and the potential adverse effects of new ARVs. In some cases, antihyperlipidemic agents may be necessary even after ARV substitution.

Appendix:

Calculations to Estimate the 10-Year Risk of Cardiac Events for Men and Women — Framingham Calculator

To calculate the 10-year risk of cardiac events, add up points from the following five tables pertaining to age, HDL, systolic blood pressure, TC, and smoking status (Tables 5.1-5.5). Note that in Tables 5.3-5.5, women's points are in parentheses. After adding points from all of the tables, consult Table 5.6. (Alternatively, an online calculator is available at cvdrisk.nhlbi.nih.gov/calculator.asp.)

(The Framingham Heart Study risk calculator has not been validated for HIV-infected individuals and may underestimate the risk in this population.)

Table 5.1. Estimate of 10-Year Risk of Cardiac Events: Age

Age (Year)	Points (Men)	Points (Women)
20-34	-9	-7
35-39	-4	-3
40-44	0	0
45-49	3	3
50-54	6	6
55-59	8	8
60-64	10	10
65-69	11	12
70-74	12	14
75-79	13	16

Table 5.2. Estimate of 10-Year Risk of Cardiac Events: High-Density Lipoprotein Cholesterol

HDL (mg/dL)	Points (Men)	Points (Women)
≥60	-1	-1
50-59	0	0
40-49	1	1
<40	2	2

Table 5.3. Estimate of 10-Year Risk of Cardiac Events: Systolic Blood Pressure

Systolic Blood Pressure	Points if Untreated — Men (Women)	Points if Treated — Men (Women)
<120	0 (0)	0 (0)
120-129	0 (1)	1 (3)
130-139	1 (2)	2 (4)
140-159	1 (3)	2 (5)
≥160	2 (4)	3 (6)

Table 5.4. Estimate of 10-Year Risk of Cardiac Events: Total Cholesterol

Total Cholesterol (mg/dL)	Points for Men (Women)				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
160-199	4 (4)	3 (3)	2 (2)	1 (1)	0 (1)
200-239	7 (8)	5 (6)	3 (4)	1 (2)	0 (1)
240-279	9 (11)	6 (8)	4 (5)	2 (3)	1 (2)
≥280	11 (13)	8 (10)	5 (7)	3 (4)	1 (2)

Table 5.5. Estimate of 10-Year Risk of Cardiac Events: Smoking Status

Smoking Status	Points for Men (Women)				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Smoker	8 (9)	5 (7)	3 (4)	1 (2)	1 (1)

Table 5.6. Estimate of 10-Year Risk of Cardiac Events: Calculating Risk

Men		Women	
Point Total	10-Year Risk (%)	Point Total	10-Year Risk (%)
<0	<1	<9	<1
0	1	9	1
1	1	10	1
2	1	11	1
3	1	12	1
4	1	13	2
5	2	14	2
6	2	15	3
7	3	16	4
8	4	17	5
9	5	18	6
10	6	19	8
11	8	20	11
12	10	21	14
13	12	22	17
14	16	23	22
15	20	24	27
16	25	≥25	≥30
≥17	≥30		

Patient Education

- Review the importance of reducing cardiovascular risk factors. This is of increasing importance for all patients with HIV infection, particularly as they age.
- Educate patients about the benefits of diet and exercise in improving lipid levels and reducing cardiovascular risk.
- If lipid-lowering medications are prescribed, advise patients on possible adverse effects, and advise them to contact their health care provider if these develop.
- Advise patients to talk with their health care provider before starting any new medications so they can be evaluated for possible drug-drug interactions.

Insulin Resistance, Hyperglycemia, and Diabetes on Antiretroviral Therapy

Background

Diabetes is a substantial risk factor for coronary artery disease, stroke, and peripheral vascular disease, as well as for a number of other conditions including retinopathy and kidney disease. Patients taking antiretroviral (ARV) medications, especially certain protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs), appear to have an increased risk of hyperglycemia and diabetes mellitus. In particular, the ARVs indinavir and stavudine (now seldom used in the United States) have been shown to induce insulin resistance in short-term studies of healthy HIV-uninfected volunteers, but other ARVs also perturb glucose homeostasis.

Disorders of glucose metabolism may present as the following:

- **Insulin resistance:** a state in which higher concentrations of insulin are required to exert normal effects; blood glucose levels may be normal but fasting insulin levels may be high because of compensatory insulin secretion by the pancreas
- **Impaired glucose tolerance:** glucose 140-199 mg/dL 2 hours after a 75 g oral glucose load
- **Impaired fasting glucose:** glucose 100-125 mg/dL after an 8-hour fast
- **Diabetes mellitus:** any of the following four criteria may be used (results must be confirmed by retesting on a subsequent occasion):
 - Fasting glucose ≥ 126 mg/dL
 - Glycosylated hemoglobin (HbA1c) level $\geq 6.5\%$ (note that HbA1c testing has not been validated in HIV-infected persons; see “Diagnostic Evaluation,” below)
 - 2-hour glucose level ≥ 200 mg/dL during glucose tolerance testing
 - Random glucose values ≥ 200 mg/dL in the presence of symptoms of hyperglycemia

The incidence of new-onset hyperglycemia among HIV-infected patients on ARV therapy (ART) has been reported as about 5%, on average. Even if fasting glucose levels remain normal in patients taking ARVs, up to 40% of those on a PI-containing regimen will show impaired glucose tolerance. The etiology of insulin resistance and hyperglycemia in HIV-infected patients probably is multifactorial, with varying contributions from traditional risk factors (e.g., obesity, family history), comorbid conditions (e.g., hepatitis C virus infection), and ARV-related factors (e.g., direct effects of PIs, cumulative exposure to NRTIs, hepatic steatosis, and fat redistribution).

Patients who have preexisting diabetes should be monitored closely when starting ART; some experts would consider avoiding PIs for these patients, if other options are feasible. Alternatively, PIs with favorable metabolic profiles (e.g., atazanavir) may be preferred for such patients. Patients with no history of diabetes should be advised about the warning signs of hyperglycemia (polydipsia, polyuria, and polyphagia) and the need to use diet and exercise to maintain an ideal body weight.

S: Subjective

Clinicians should consider the potential for abnormal glucose metabolism in the following types of patients:

- Those who are about to begin ART
- Those on an ARV regimen that includes a PI
- Those with extensive exposure to NRTIs
- Those who are obese or overweight
- Those with central fat accumulation or lipoatrophy

Although most patients with hyperglycemia are asymptomatic, some (rarely) may report polydipsia, polyuria, polyphagia, or blurred vision.

When recording the patient's history, ask about the following:

- **Risk factors:**
 - Family history of diabetes
 - Obesity
 - Habitual physical inactivity
 - Racial or ethnic heritages (higher risk: African-American, Hispanic, Native American, Asian/Pacific Islander)
 - Gestational diabetes or delivery of an infant weighing >9 lb (4.1 kg)
 - Current pregnancy
 - Hepatitis C virus coinfection
 - Polycystic ovary syndrome
 - Medications, including PIs, NRTIs, niacin, corticosteroids, antipsychotics
- **Comorbidities:**
 - Hypertension
 - Low level of high-density lipoprotein (HDL)
 - Elevated triglycerides
 - Coronary artery disease
 - Fat redistribution on ARVs (see chapter *Abnormalities of Body-Fat Distribution*)
 - Smoking

O: Objective

Perform a physical examination that includes the following:

- Blood pressure, weight, body mass index (BMI) (see chapter *Dyslipidemia*)
- Heart and lung examination
- Peripheral pulses
- Examination of neck, dorsocervical area, breasts, and abdomen for fat accumulation; measurement of waist circumference
- For patients with hyperglycemia or diabetes:
 - Retinal examination (refer to ophthalmologist for dilated examination)
 - Visual inspection of feet (for ulcers)
 - Sensory examination of feet (for neuropathy)

A/P: Assessment and Plan

Diagnostic Evaluation

Determine whether the patient has normal blood glucose, impaired fasting glucose, or diabetes.

Most experts recommend routine checks of fasting blood glucose levels at baseline and within 3-6 months after starting or changing ART, if baseline results are normal. For patients with normal glucose levels, recheck every 6-12 months. Monitoring should be more frequent if abnormalities are detected or if any additional risk factors exist. Patients with risk factors for diabetes must be counseled about prevention of hyperglycemia before starting ART.

The role of 2-hour postprandial glucose measurements or the 75 g oral glucose tolerance test for diabetes is uncertain but these screenings may be appropriate for patients with multiple risk factors. The use of HbA1c testing to screen for diabetes has yet to be validated for the HIV-infected population. Of note, HbA1c values may underestimate glycemia in HIV-infected patients, especially

in the setting of elevated red blood cell mean corpuscular volume (MCV) (e.g., owing to zidovudine) or anemia.

For patients with diabetes, monitor the following:

- HbA1c, every 3 months for patients who have elevated HbA1c or whose therapy has changed, every 3-6 months for patients with stable and adequate glucose control
- Fasting lipid panel
- Electrolytes, creatinine, estimated glomerular filtration rate (eGFR) (see chapter *Renal Disease*)
- Urine albumin/creatinine ratio (microalbuminuria: 30-299 mg/g)

Treatment

Patients with insulin resistance

For patients with insulin resistance who have normal blood glucose levels, current evidence is inadequate to recommend drug treatment. However, it may be possible to prevent the development of diabetes, and lifestyle modifications can be recommended, including exercise, avoidance of obesity, weight loss if indicated, and diet changes. Weight loss is strongly recommended if the patient is overweight. Refer the patient to a dietitian, if possible. Studies of insulin resistance in HIV-infected individuals are under way, and patients with access to clinical trials may be referred to these studies.

Patients with insulin resistance and hyperglycemia require treatment. A trial of lifestyle modifications may be attempted, including weight loss (if indicated), diet changes, and exercise.

For patients with diabetes and those whose lifestyle changes are not adequate to control blood glucose, specific treatment should be started.

Patients with diabetes

- Treatment should be instituted to control blood sugar and to modify other cardiovascular risk factors, with the aim of preventing heart disease and other end-organ disease.
- Control glucose: maintain the HbA1c level at <7%, while avoiding hypoglycemia.
- For hyperglycemia that is associated with the use of PIs, switching to an alternative agent (e.g., a nonnucleoside reverse transcriptase inhibitor, an integrase inhibitor, or a different PI) may be effective if the HIV treatment history and resistance profile permit.
- Metformin usually is the initial drug of choice for overweight patients; other options include sulfonylureas and thiazolidinediones.
- Metformin can worsen lipoatrophy and should be avoided in the presence of significant lipoatrophy. Metformin increases risk of lactic acidosis; it should not be used for patients with elevated serum creatinine (>1.5 mg/dL in men or >1.4 mg/dL in women), hepatic impairment, or metabolic acidosis.
- Sulfonylureas may cause hypoglycemia. In starting therapy, shorter-acting agents (e.g., glipizide) may be preferable to longer-acting agents (e.g., glyburide). Some agents should not be used for patients with renal impairment (CrCl <50 mL/min).
- Thiazolidinediones should be avoided in patients with significant liver disease. Rosiglitazone may increase the risk of myocardial infarction and death (study results conflict); both rosiglitazone and pioglitazone have been associated with congestive heart failure and are contraindicated for use by patients with this condition.

- In some cases, insulin may be the safest drug therapy for patients with symptomatic hyperglycemia, although episodes of hypoglycemia are much more common with insulin than with most oral agents.
- Treat dyslipidemia: maintain low-density lipoprotein (LDL) at <100 mg/dL and maintain triglycerides at <150 mg/dL. (Note that diabetes is considered a coronary heart disease equivalent state when evaluating goals for lipid management; see chapter *Dyslipidemia*.)
- Treat hypertension: Maintain systolic blood pressure at <130 mm Hg and diastolic blood pressure at <80 mm Hg.
- Reduce cardiovascular risks through lifestyle modifications such as smoking cessation, exercise, weight loss, nutritional counseling, and moderation of alcohol intake.
- Decrease the risk of end-organ complications:
 - Measure urine microalbumin and creatinine; if the urine albumin/creatinine ratio is >30 mg/g, treat with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) to slow the progression of nephropathy.
 - Schedule annual retinal examination by an ophthalmologist.
 - Perform an annual foot examination.
- Start aspirin therapy (75-162 mg daily) if the patient has evidence of macrovascular disease or a history of vascular events. Consider daily aspirin for those with increased coronary heart disease risk (e.g., men >50 years and women >60 years of age with ≥1 coronary heart disease risk factor, such as a family history of coronary artery disease or a history of smoking) (see chapter *Coronary Heart Disease Risk*).

For further information, see the American Diabetes Association, Clinical Practice Recommendations, Diabetes Care, available at care.diabetesjournals.org.

Patient Education

- ART can increase the risk of diabetes in some individuals. Patients should report any difficulty with excessive hunger and thirst and increased urination. Health care providers will monitor blood glucose when doing laboratory work, but it is important for the patient to report the presence of any symptoms.
- Review the patient's eating habits and explain the need to work with a dietitian to keep blood glucose (and triglycerides) within normal limits. Eating a proper diet can reduce the risk of permanent damage to the blood vessels of the eye, the kidney, and the brain, and it can reduce the risk of a heart attack.
- Emphasize other lifestyle modifications, such as weight loss (if appropriate).
- Encourage patients to get regular cardiovascular exercise; work with them to identify activities that might be realistic and acceptable for them.
- Provide medication-specific education, especially if the patient will be taking diabetes medications.
- Consider referral to a diabetes clinic for specialty needs.

Coronary Heart Disease Risk

Background

Epidemiologic studies suggest that the incidence of myocardial infarction or hospitalization for coronary heart disease (CHD) is increased up to twofold in HIV-infected individuals compared with age-matched controls without HIV infection. This increased risk of ischemic events likely is attributable to a higher prevalence of certain CHD risk factors that are independent of HIV status, such as smoking, as well as to both HIV infection and antiretroviral (ARV) medications. These various factors may interact in ways that are complex and incompletely understood.

Among the traditional CHD risk factors, dyslipidemia is common among persons with HIV infection, and can be caused both by HIV itself (e.g., resulting in low high-density lipoprotein [HDL] cholesterol) and by ARV therapy (ART); see chapter *Dyslipidemia*. Insulin resistance and diabetes also appear to be more prevalent in HIV-infected patients. (See chapter *Insulin Resistance, Hyperglycemia, and Diabetes on Antiretroviral Therapy*.) Visceral fat accumulation, a poorly understood complication of HIV or ART, also may contribute to CHD risk in certain patients (see chapter *Abnormalities of Body-Fat Distribution*).

Several studies have suggested that low CD4 cell counts are associated with myocardial infarction and stroke. Additionally, a number of studies suggest that inflammation and immune activation owing to uncontrolled HIV infection also likely contribute to atherosclerosis. For example, in the Strategic Management of Antiretroviral Therapy (SMART) study, CHD events were more common in patients on intermittent ART than in those on continuous ART, possibly because of adverse effects of intermittent HIV viremia on inflammation, coagulation, and lipid parameters. There is even preliminary evidence that so-called elite controllers – patients with undetectable HIV viremia and preserved CD4 counts in the absence of ART – have increased carotid intima-medial thickness (a marker of atherosclerotic burden) compared with HIV-uninfected subjects, after adjusting for other CHD risk factors. Limited data also suggest that initiation of ART leads to improvement of endothelial dysfunction (an early marker of atherosclerosis that is predictive of future CHD events) and to improvement in markers of inflammation and immune activation. Taken together, these observations suggest that earlier initiation of ART could reduce CHD risk.

On the other hand, even patients with virologic suppression on ART appear to have higher levels of various physiologic markers of cardiovascular risk than the HIV-uninfected persons, perhaps owing to persistent immune activation. Additionally, exposure to ARVs has been linked to risk of myocardial infarction in large cohort studies such as the D:A:D study. In particular, the risk has been associated with use of ARV regimens that are based on protease inhibitors (PIs) rather than nonnucleoside reverse transcriptase inhibitors (NNRTIs). The risk is attributable in part to adverse changes in lipid profiles, but there appears to be additional risk associated with PIs that is not accounted for by changes in lipids; this remains poorly understood. Among the nucleoside reverse transcriptase inhibitors (NRTIs), abacavir and didanosine have been associated with increased risk of myocardial infarction in some but not all studies. The mechanism of this potentially increased risk has not been determined.

S: Subjective

Clinicians should ask all patients about CHD, CHD risk equivalents, and CHD risk factors. Assess the following during the history:

- Age (>45 for men, >55 for women)
- History of angina, myocardial infarction, or other heart disease
- Family history of premature CHD in first-degree relatives (men aged <55, women aged <65) and diabetes mellitus
- Smoking history
- Glucose intolerance or diabetes mellitus
- Hypertension
- Dyslipidemia
- CHD risk-equivalent states:
 - Diabetes mellitus
 - Peripheral vascular disease
 - Cerebrovascular disease
 - Abdominal aortic aneurysm
- Use of cocaine or amphetamines
- Physical inactivity

O: Objective

Perform a physical examination to include the following:

- Vital signs, including blood pressure, pulse, weight, and body mass index (BMI); see chapter *Dyslipidemia*
- Jugular venous distention
- Heart and lung examination
- Auscultation for carotid or femoral bruits
- Peripheral pulses and evaluation of extremities for peripheral edema
- Abdominal examination for fat accumulation, ideally with measurement of waist circumference

A: Assessment

- Determine whether the patient has established CHD or a CHD risk-equivalent state (see above).
- Stratify risk based on the number of CHD risk factors and the Framingham risk calculator if two or more major CHD risk factors are present. The risk calculator is available at cvdrisk.nhlbi.nih.gov/calculator.asp.
- Check fasting lipids and glucose annually; more frequently if abnormal.
- Patients with established or suspected CHD should undergo standard evaluations such as electrocardiography and exercise stress testing; refer to a cardiologist as appropriate.

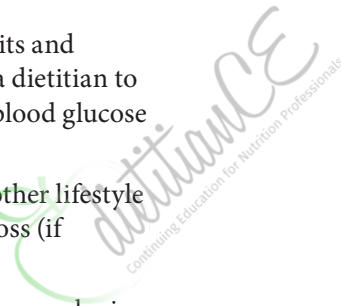
P: Plan

- Work closely with patients to reduce their risks of CHD events.
- For patients who smoke, smoking cessation is the single most important intervention to reduce risk of CHD events (see chapter *Smoking Cessation*).
- Manage dyslipidemia according to established guidelines (see chapter *Dyslipidemia*).
- Manage hypertension by lifestyle intervention (e.g., sodium restriction, exercise, weight loss) and pharmacologic therapy as indicated.
- Optimize glycemic control in patients with diabetes mellitus (see chapter *Insulin Resistance, Hyperglycemia, and Diabetes on Antiretroviral Therapy*).
- Encourage weight loss in overweight and obese patients, with referral to a dietitian as appropriate.
- Encourage exercise, ideally 30 minutes at moderate intensity 5-6 times per week.
- Encourage a healthy diet that is low in saturated fats.

- Consider aspirin 81 mg QD for primary prevention of CHD in patients at moderate to high risk who do not have contraindications to aspirin use.
- For patients who use cocaine or amphetamines, encourage cessation.

Patient Education

- Both HIV infection and ARV medications may contribute to the risk of CHD, and the available data suggest that the risk of CHD is increased in HIV-infected patients relative to the general population.
- Review the benefits of smoking cessation.
- Review exercise possibilities to determine which activities might be realistic and acceptable for the patient.
- Review the patient's eating habits and explain the need to work with a dietitian to optimize lipid levels and keep blood glucose within normal ranges.
- Emphasize the importance of other lifestyle modifications, such as weight loss (if appropriate).
- Educate patients about any pharmacologic therapy that is indicated.



Renal Disease

Background

The prevalence of renal complications among patients with HIV infection has increased as more patients with HIV are living longer as a result of effective antiretroviral therapy (ART) and opportunistic infection prophylaxis. More widespread access to and earlier initiation of ART has decreased the incidence of HIV-associated nephropathy (HIVAN), but other causes of renal disease persist, and in some cases are increasing in prevalence. These may be infections and other conditions related to HIV infection, other comorbidities (e.g., hypertension, diabetes), or medication adverse effects, including those caused by some antiretroviral (ARV) medications (see “Kidney disease associated with HIV infection” and Table 2, below).

Risk factors for renal disease in HIV-infected patients include the following:

- CD4 count <200 cells/ μ L
- HIV viremia, particularly RNA levels >4,000 copies/mL
- African-American race
- Family history of kidney disease
- Use of nephrotoxins (including medications; see Table 2, below)
- Comorbidities
 - Diabetes mellitus
 - Hypertension
 - Hepatitis C

Renal disease in HIV-infected individuals can occur as a primary disease, as a secondary disease in the setting of other systemic illness, or as an adverse effect of medications. In the United States, the most common causes of end-stage renal disease in the general population are diabetes mellitus and hypertension. HIV-infected patients are at a fourfold higher risk of developing diabetes mellitus and a threefold higher risk of developing hypertension compared with seronegative individuals. Chronic hepatitis C, seen in 30-40% of HIV-infected individuals in the United States, is associated with several types of chronic kidney disease, including progressive secondary glomerulonephropathy, membranoproliferative glomerulonephropathy, and mixed cryoglobulinemia.

Note that ART should be given to HIV-infected individuals with renal disease, according to usual criteria for ART initiation; however, some ARVs must be avoided and some should be given at modified dosages according to the degree of renal dysfunction (see Table 3). Additionally, for patients with HIVAN, ART is the primary treatment.

Screening

Screening for kidney disease in HIV-infected persons is an important aspect of primary care, as patients typically have no symptoms until very late. High-risk patients (see list of risk factors, above) should be identified and monitored. Early identification of patients with renal dysfunction allows early intervention targeted at reversing the process of renal injury or slowing its progression. Current guidelines of the U.S. Department of Health and Human Services (HHS) and the Infectious Diseases Society of America recommend screening at entry to care, with subsequent screening as indicated by the patient's risk factors.

Screening consists of three tests:

- **Serum creatinine (Cr) and calculated estimate of renal function (eGFR);** the eGFR usually is provided by the laboratory but may be calculated as follows:

- *eGFR by the Modification of Diet in Renal Disease (MDRD) equation:*

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 186 \times [\text{serum Cr (mg/dL)}]^{-1.154} \times [\text{age (years)}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if African-American}]$$

Normal GFR: $\geq 90 \text{ mL/min/1.73 m}^2$

Chronic kidney disease (CKD): $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$

An online eGFR calculator is available at www.nkdep.nih.gov/lab-evaluation/gfr-calculators.shtml.

- The creatinine clearance (CrCl) can be used as a surrogate for eGFR but is considered to be less accurate. Note that CrCl is used in determining medication dosages.

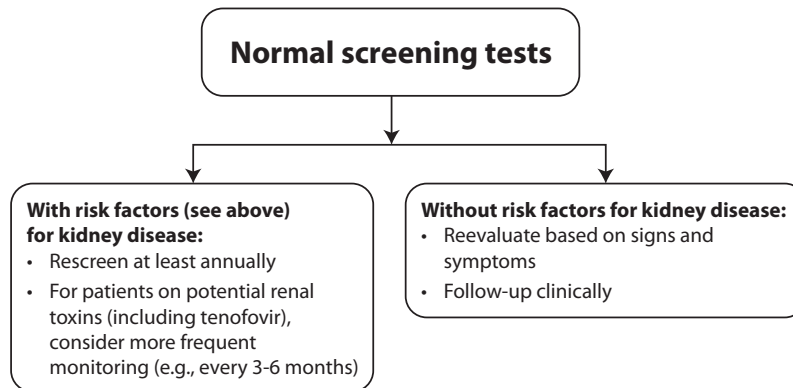
CrCl (Cockcroft-Gault equation):

$$\frac{(140 - \text{age}) \times (\text{weight in kilograms})}{72 \times \text{serum Cr (mg/dL)}}; \text{ multiply by } 0.85 \text{ for females}$$

- **Urinalysis, for proteinuria, hematuria**
- **Quantitative test for proteinuria** (if $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$ or $\geq 1+$ protein on dipstick):
 - Random urinary protein to urinary Cr ratio (U Pr/U Cr)
 - This estimates 24-hour protein excretion and correlates well with grams per day of proteinuria; for example, a random U Pr/U Cr of 1.0 correlates with 1 g/day of proteinuria (normal is ≤ 0.2)

Suggested follow-up for patients with normal screening test results is shown in Figure 1; suggested follow-up of abnormal screening test results is shown in "Diagnostic Evaluation."

Figure 1. Follow-Up for Patients with Normal Screening Test Results



S: Subjective

As noted above, patients usually have no symptoms until late in the course of kidney disease and are diagnosed on the basis of laboratory abnormalities.

In symptomatic patients, presenting signs or symptoms are nonspecific. Patients with renal failure may present with fatigue, weakness, anorexia, nausea, pruritus, vomiting, edema, diminished urine output, discolored urine, altered mental status, and seizures. Those with renal disease associated with systemic illnesses may present with fever, arthralgias, respiratory symptoms, flank pain, abdominal pain, and diarrhea.

For patients with renal disease suspected on the basis of laboratory abnormalities (e.g., elevated serum Cr [azotemia], electrolyte disturbances, acid-base disorders, proteinuria, hematuria, and anemia), and for symptomatic patients with known kidney disease, ask about the risk factors and symptoms described above, and about the following:

- Systemic illness
 - Night sweats, fever, weight loss
 - Shortness of breath, cough, hemoptysis, nasal congestion, rhinorrhea
 - Diarrhea, hematochezia, melena
 - Dysuria, frequency, urgency, polyuria, decreased urine output, discoloration of urine
- Skin rash or skin lesions
- Edema, arthralgias, painful swollen joints, myalgias
- Family history of kidney disease, hypertension, diabetes mellitus
- Recent radiographic imaging with IV contrasts (including those containing gadolinium or iodinated agents)

Review the patient's medication list (see Table 1).

- Include over-the-counter medications, nonsteroidal antiinflammatory drugs, phosphate-containing enemas

O: Objective

Check blood pressure, temperature, and weight. Compare these with values from previous readings. Perform a physical examination, including evaluations of the following:

- Volume status (blood pressure, pulse, skin turgor, mucous membrane moistness, edema)
- Optic fundi (signs of retinopathy)
- Cardiovascular system (peripheral pulses, bruits), to assess for peripheral vascular disease
- Abdomen (auscultate for unilateral bruit [renal artery stenosis], distention, mass, organomegaly, tenderness)
- Musculoskeletal system (bruises, muscle pain, muscle weakness, swollen joints)
- Skin (rash to help evaluate for drug reaction, vasculitis)
- Rectum (enlarged prostate, if obstruction is suspected)

Review previous laboratory values (e.g., serum Cr, blood urea nitrogen [BUN], electrolytes, urinalysis) to determine whether the kidney disease is acute or chronic.

- Acute kidney injury (AKI) is assumed if there are no previous serum Cr values.

The presence of an abnormal GFR (≤ 60 mL/min for at least 3 months) suggests chronic kidney disease (CKD).

Review the CD4 cell count and HIV viral load.

A: Assessment

Once the duration of the elevated serum Cr is assessed, a differential diagnosis can be made.

The causes of renal failure are classified traditionally based on the area of the renal anatomy where the injury occurred: prerenal, renal, and postrenal (obstructive uropathy). Acute tubular necrosis (ATN) is the most common cause of acute kidney injury.

Table 1. Causes of Renal Failure

Prerenal	Renal	Postrenal
Laboratory Data		
<ul style="list-style-type: none">• Urine sodium (Na) <30 mEq/L• Fractional excretion of Na (FeNa) $<1\%$ (see below)• Fractional excretion of urea $<35\%$• Serum BUN: serum Cr ratio ≥ 20	<ul style="list-style-type: none">• Urine Na >30 mEq/L• FeNa $>1\%$ (see below)• Fractional excretion of urea >50• Serum BUN: serum Cr ratio ≥ 10	<ul style="list-style-type: none">• Hematuria• Imaging showing obstruction

Prerenal	Renal	Postrenal
Partial Differential Diagnosis		
<p>Decreased renal perfusion</p> <ul style="list-style-type: none"> • Volume depletion • Effective volume depletion <ul style="list-style-type: none"> • Heart failure • Cirrhosis • Shock <p>Vascular disease</p> <ul style="list-style-type: none"> • Renal artery stenosis <p>Medication induced</p> <ul style="list-style-type: none"> • Prostaglandin inhibition (NSAID) • ACE inhibitors and angiotensin receptor blockers 	<p>Acute Tubular Necrosis</p> <p>Ischemia leading to ATN</p> <ul style="list-style-type: none"> • Prolonged hypotension attributable to any cause <ul style="list-style-type: none"> • Sepsis syndrome • Volume depletion (gastrointestinal bleeding) • Atheroembolism and thromboembolism • Systemic vasculitis • Thrombotic microangiopathy (TTP, HUS) <p>Endogenous toxins</p> <ul style="list-style-type: none"> • Myoglobin (rhabdomyolysis) • Uric acid and calcium-phosphate complexes (tumor lysis syndrome) <p>Exogenous-induced ATN</p> <ul style="list-style-type: none"> • Aminoglycosides • Amphotericin B • Foscarnet • Ganciclovir • Intravenous pentamidine • Tenofovir • Chemotherapeutic agents (methotrexate, cisplatinum) <p>Glomerulonephropathy</p> <ul style="list-style-type: none"> • Many specific types; some associated with HIV (including HIVAN) or associated infections and other conditions <p>Other intrarenal lesions</p> <ul style="list-style-type: none"> • Acute interstitial nephritis (AIN) • Drug induced • Infections associated with AIN <ul style="list-style-type: none"> • Bacterial (<i>Streptococcus</i>, <i>Mycobacteria</i>, <i>Legionella</i>, <i>Pneumococcus</i>) • Viral (Epstein-Barr, herpes simplex type 1, cytomegalovirus, BK virus) • Fungal (histoplasmosis, candidiasis) • Other infections (toxoplasmosis, syphilis, schistosomiasis, malaria, leptospirosis) • Infectious <ul style="list-style-type: none"> • Granulomatous (mycobacterial disease, coccidioidomycosis, histoplasmosis) • Tumors <ul style="list-style-type: none"> • Multiple myeloma • Lymphoma • Nephrolithiasis • Intratubular obstruction <ul style="list-style-type: none"> • Drug-induced crystalluria <ul style="list-style-type: none"> ▶ Antiviral (acyclovir, indinavir, atazanavir) ▶ Antibiotic (trimethoprim/sulfamethoxazole) 	<p>Prostate hypertrophy</p> <p>Tumors</p> <p>Stones or crystal deposition</p>

Kidney Disease Associated with HIV Infection

A discussion of glomerulonephropathy is beyond the scope of this chapter, but HIV and associated comorbidities (e.g., infections such as hepatitis C, hepatitis B, and cytomegalovirus, along with malignancies, heroin use, nephrotoxic medications, diabetes mellitus, and hypertension) are among the many causes of glomerulonephropathy. The condition most closely associated with HIV is HIVAN. This is a collapsing focal segmental glomerulosclerosis (FSGS) that usually occurs in persons of African heritage, and particularly those with a low CD4 count or high HIV RNA level. The clinical presentation includes the following:

- Nephrotic syndrome or nonnephrotic proteinuria
- Normal blood pressure
- Elevated Cr, often with rapid progression to end-stage renal disease (<6 months)
- Renal ultrasound usually reveals normal size or slightly enlarged echogenic kidneys
- Renal biopsy shows a collapsing FSGS

In addition, several conditions may be caused by ARV medications. Tenofovir may cause, though rarely, AKI with type 2 renal tubular acidosis (RTA) and Fanconi syndrome.

Alternatively, it more commonly causes a gradual increase in serum Cr over a period of months or years; this appears to occur more frequently in persons concomitantly taking ritonavir-boosted PIs and perhaps also in those taking cobicistat. Patients who take tenofovir should have renal function monitored every 3-6 months. Indinavir can cause crystalluria, nephrolithiasis, and acute interstitial nephritis, and atazanavir can cause nephrolithiasis.

Some other medications commonly used in the treatment of patients with HIV infection and associated conditions may cause acute or chronic kidney injury. See Table 1, above, and Table 2, below.

It should be noted that several ARVs (including the NNRTI rilpivirine and the integrase inhibitor dolutegravir) as well as the pharmacokinetic inhibitor cobicistat (in the coformulation elvitegravir/cobicistat/tenofovir/emtricitabine, Stribild) may inhibit renal tubular secretion of creatinine and thus cause modest increases in serum Cr (in the range of 0.1-0.2 mg/dL) and modest decreases in eGFR. This does not result from kidney injury, and actual GFR remains stable. These creatinine increases occur in the initial weeks of treatment with one of these agents and remain stable afterward (if increases in Cr exceed what is expected for these drugs, it is important to conduct an evaluation for other causes).

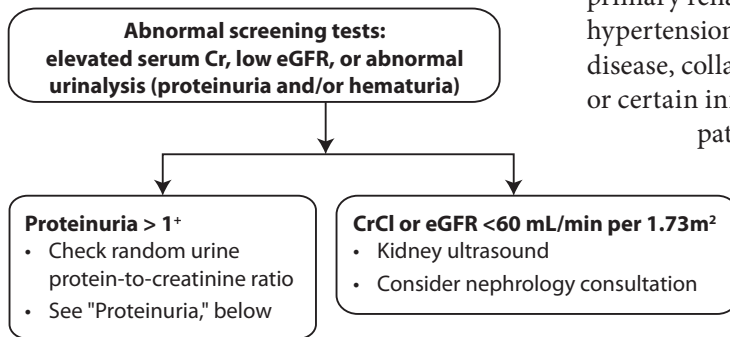
Table 2. Selective Drugs Causing Acute or Chronic Kidney Injury in HIV-Infected Patients

Drugs	Acute Tubular Necrosis	Acute Interstitial Nephritis	Other Associated Abnormalities
Antiretroviral Medications			
Abacavir		+/-	
Atazanavir		+	Nephrolithiasis
Indinavir		+	Crystalluria
Tenofovir	+		Fanconi syndrome (hypokalemia, non-gap metabolic acidosis, hypophosphatemia, glycosuria) May cause a slow increase in Cr
Other Medications			
TMP-SMX (Bactrim, Septra)		+++	Hyperkalemia, crystalluria
Beta-lactams		++	
Sulfonamides		++	
Fluoroquinolones		+	
Aminoglycosides (e.g., streptomycin, gentamycin, amikacin)	+++		
Rifampin	+	+	
Isoniazid		+	Overdose leads to high anion gap metabolic acidosis
Dapsone	+/-		Papillary necrosis
Amphotericin B	+++		Hypokalemia, hypernatremia (nephrogenic diabetes insipidus)
Pentamidine	+++		Crystalluria
Foscarnet	+++		
Ganciclovir	+		
Acyclovir	+		Crystalluria
NSAIDs		+	Proteinuria, secondary minimal change disease, papillary necrosis

P: Plan

Diagnostic Evaluation

Figure 2. Workup of Abnormal Screening Test Results



Determine whether the renal disease is acute or chronic, as above (see “O: Objective”).

Perform a targeted laboratory evaluation, depending on results of initial tests, history, and physical examination.

- Urinalysis with microscopy and examination of urine sediment (e.g., hematuria, pyuria, casts) can help in identifying etiologies such as nephritic syndrome, ATN, or infection.
- Quantify the proteinuria by obtaining a random urine protein-to-urine creatinine ratio (U Pr/U Cr), if not done already; this correlates well with grams per day of proteinuria, as discussed above.
- Fractional excretion of sodium (FeNa) may be helpful in distinguishing causes of acute kidney injury.
 - $$\text{FeNa} = \frac{\text{Urine sodium} \div \text{Serum sodium}}{\text{Urine Cr} \div \text{Serum Cr}}$$
 - FeNa <1 is highly suggestive of prerenal state
 - FeNa >1 is suggestive of intrinsic renal injury
- Urine culture, if urinary tract infection is suspected

Further workup will depend on the findings and the suspected cause.

Proteinuria

Proteinuria can be present in patients with primary renal disease, and also in those with hypertension, diabetes mellitus, vascular disease, collagen vascular disease, malignancy, or certain infections. Proteinuria is not always pathologic and may be caused by

transient conditions such as pregnancy, strenuous exercise, fever, seizure, or congestive heart failure; in some cases, it may be benign.

However, proteinuria should be evaluated if it persists. If present with hematuria, proteinuria is highly suspicious for a glomerular disease.

The major classifications of persons with proteinuria are as follows:

Nephrotic syndrome:

- >3.5 g/day proteinuria
- “Bland” sediment, with no or few red or white blood cells
- Edema
- Hyperlipidemia
- Hypoalbuminemia
- Check serum complements (C3 and C4):
 - Low complements: glomerulonephritis associated with subacute bacterial endocarditis, infection (postinfectious), lupus, membranoproliferative glomerulonephritis, and mixed cryoglobulinemia

Glomerulonephritis:

- Proteinuria
- “Active” sediment, with white and red blood cells; may see red blood cell casts
- Further categorized into those with normal renal function and those with abnormal renal function

Hematuria

For asymptomatic isolated microscopic hematuria, obtain a follow-up urinalysis. If hematuria is persistent, obtain a renal and bladder ultrasound. If the result is normal, the eGFR is normal, and there are no other urine abnormalities, conduct routine follow-up with urinalysis and serum Cr testing. Refer patients aged ≥ 40 with persistent hematuria to a urologist for formal evaluation. Consider checking urine cytology, though that test is not sensitive enough to rule out genitourinary malignancy.

Red blood cell casts

Red blood cell casts strongly suggest glomerulonephritis, which can progress rapidly.

ATN

ATN is the most common cause of AKI. A history of certain medication exposures, recent IV contrast, and concurrent illness may provide important clues to ATN. Laboratory findings that are consistent with ATN include increasing serum Cr and a characteristic urine sediment that shows “muddy brown” casts, which are casts that contain densely packed tubular cells.

AIN

During AIN, the classic triad of AKI, fever, and rash is not always present. Laboratory findings suggestive of AIN in the setting of AKI include sterile pyuria and eosinophiluria.

Sterile pyuria

Sterile pyuria also may occur in malignancy (e.g., renal, bladder), and in genitourinary tuberculosis. If tuberculosis is suspected, further testing usually requires three first-void urine specimens sent for acid-fast bacilli culture.

Crystalluria and nephrolithiasis

Usual causes of nephrolithiasis should be considered in patients with hematuria, particularly if symptoms consistent with nephrolithiasis are present. Other causes in

persons with HIV infection include some medications, including the ARVs indinavir and (rarely) atazanavir; see Table 2 above.

Obtain radiographic imaging (see below) as part of the initial evaluation, and send the passed renal stone, if available, for analysis in order to provide more specific recommendations for management. If there is suspicion that the condition is caused by a medication, order specific chemical analysis (e.g., for atazanavir).

In patients with multiple renal stones, active renal stone formation, and recurrent kidney stones, a metabolic evaluation should be done. This includes a serum intact parathyroid hormone measurement and 24-hour urine collection for Cr, sodium, calcium, oxalate, uric acid, and citrate.

Imaging

Radiographic imaging of the kidneys is important in the evaluation of renal disease. The size and echogenicity of the kidneys may help differentiate acute and chronic kidney disease. Small and echogenic kidneys are consistent with CKD, though HIV, diabetes, and some other chronic conditions are associated with normal size or large kidneys. Imaging also helps identify obstruction (though the absence of hydronephrosis does not completely rule that out), malignancy, and other conditions.

Both spiral computed tomography (CT) scan and renal ultrasound are acceptable radiographic imaging studies for nephrolithiasis. The advantage of spiral CT scan is its ability to localize stones and assess their size without the use of contrast. Gallium renal scan may be helpful in AIN.

Renal biopsy

Biopsy is not always indicated for patients with renal disease, but it can be very helpful in establishing some diagnoses and determining treatment options.

Treatment

Patients with proteinuria will benefit from angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Follow the serum potassium and Cr during treatment with an ACEI or ARB (check 1 week after initiation, then periodically). Follow the JNC VII (Joint National Committee on Prevention, Detection, Evaluation and Treatment of Blood Pressure) guidelines for blood pressure control. For patients with hypertension and proteinuria, the target blood pressure is <125/80 mm Hg.

The cornerstone of HIVAN management is fully suppressive ART, and this should be quickly initiated or optimized in all patients, if possible. An ACEI or ARB also should be used to treat proteinuria. A trial of corticosteroids can be considered for patients with deteriorating kidney function while on effective ART plus an ACEI or ARB; consult with a specialist.

For ATN and AIN, discontinue the offending medications and provide supportive care, which may include gentle volume repletion, replacement of bicarbonate deficit, and management of electrolyte abnormalities (e.g., hyperkalemia); consult with a renal specialist.

Other modalities of treatment such as steroids or immunomodulators may be needed, depending on the specific glomerular disease diagnosed by renal biopsy.

Uncomplicated nephrolithiasis can be managed with hydration and pain control. Oral fluid intake should be titrated to produce ≥ 2 liters of urine output per day. Recommendations for dietary modifications should be based on the 24-hour urine metabolic evaluation. A low-calcium diet usually is not helpful for patients with normal serum calcium and may be detrimental to patients with oxalate renal stones. If the crystalluria is caused by medications, discontinue the offending medications, if possible (in the case of ARBs, make substitutions to maintain optimal virologic suppression).

Patients with complicated nephrolithiasis or pyelonephritis require urgent urologic evaluation.

Follow-Up

- Acute kidney injury
 - Monitor serum electrolytes, BUN and Cr
 - After these normalize, perform routine follow-up
- Acute interstitial nephritis
 - Avoid offending medications
- Chronic kidney disease
 - Follow blood pressure closely
 - If hypertensive, consider an ACEI or ARB as first-line medication, as above
 - Target blood pressure is <130/80 mm Hg
 - If evidence of nephropathy, target blood pressure is <125/75 mm Hg
 - For patients with diabetes, optimize blood glucose control
 - Address other risk factors for cardiovascular disease (see chapter *Coronary Heart Disease Risk*)
 - Dyslipidemia
 - Cigarette smoking
 - Obesity
 - Physical inactivity
 - Monitor serum electrolytes, BUN, Cr, and hemoglobin
 - Risk of secondary hyperparathyroidism:
 - Serum calcium <9.5 mg/dL
 - Parathyroid hormone level >35 pg/mL
 - Management:
 - Low-phosphate diet
 - Phosphate binders with meals
 - Vitamin D supplement

- Anemia
 - Consider recombinant human erythropoietin and iron supplement (consult with a nephrologist)
 - Target hemoglobin 11-12 g/dL
 - Avoid nephrotoxins, if possible
 - Adjust medication dosages based on renal function (eGFR); see below
- Patients with severe or chronic renal disease should be referred to Nephrology for further evaluation and assistance with the following:
- Management
 - Education
 - Evaluation for renal replacement therapy
 - Peritoneal dialysis
 - Hemodialysis
 - Kidney transplant evaluation
- Medication Dosage Adjustment**

Dosages of many medications, including most nucleoside analogues (NRTIs), must be adjusted for patients with CKD, and for those on hemodialysis; see Table 3, below.

Table 3. Dosing of Antiretroviral Drugs in Adults with Chronic Kidney Disease and Hemodialysis

Drug	Standard Dosage	Dosing in Chronic Kidney Disease and Hemodialysis		
Abacavir	300 mg PO BID	Dosage adjustment for CKD does not appear necessary		
Didanosine (enteric-coated capsules)	250 mg to 400 mg PO QD, depending on weight	CrCl (mL/min)	Weight ≥60 kg	Weight <60 kg
		≥60	400 mg QD	250 mg QD
		30-59	200 mg QD	125 mg QD
		10-29	125 mg QD	125 mg QD
		<10	125 mg QD	Formulation not suitable
		HD	125 mg QD	Formulation not suitable
Emtricitabine	200 mg PO QD	CrCl (mL/min)		
		≥50	200 mg QD	
		30-49	200 mg Q48H	
		15-29	200 mg Q72H	
		<15	200 mg Q96H	
		HD	200 mg Q96H, take after dialysis	
Lamivudine 150 mg PO BID or 300 mg PO QD	150 mg PO BID or 300 mg PO QD	CrCl (mL/min)		
		≥50	150 mg BID or 300 mg QD	
		30-49	150 mg QD	
		15-29	150 mg first dose, then 100 mg QD	
		5-14	150 mg first dose, then 50 mg QD	
		<5	50 mg first dose, then 25 mg QD	
		HD	50 mg first dose, then 25 mg QD, take after dialysis	
Stavudine	20 mg to 40 mg PO BID, depending on weight	CrCl (mL/min)	Weight ≥60 kg	Weight <60 kg
		>50	40 mg BID	30 mg BID
		26-50	20 mg BID	15 mg BID
		10-25	20 mg QD	15 mg QD
		HD	20 mg QD, take after dialysis	15 mg QD, take after dialysis

Drug	Standard Dosage	Dosing in Chronic Kidney Disease and Hemodialysis	
Tenofovir	300 mg PO QD	Experience in patients with CrCl <60 mL/min is limited.	
		CrCl (mL/min)	
		≥50	300 mg QD
		30-49	300 mg Q48H
		10-29	300 mg BIW (i.e., Q 3-4 days)
		<10	Not recommended
		HD	300 mg once weekly, after dialysis
Zidovudine	300 mg PO BID	CrCl (mL/min)	
		<15	100 mg TID (or 300 mg QD)
		HD	100 mg TID (or 300 mg QD); take after dialysis

Fixed-Dose Combinations

Drug	Standard Dosage	Dosing in Chronic Kidney Disease and Hemodialysis	
Atripla (efavirenz/tenofovir/emtricitabine)	1 tab PO QHS	Substitute component drugs, adjusting dosage of each drug for CrCl	
Combivir (zidovudine/lamivudine)	1 tab PO BID	Substitute component drugs, adjusting dosage of each drug for CrCl	
Complera (rilpivirine/tenofovir/emtricitabine)	1 tab PO QD	Substitute component drugs, adjusting dosage of each drug for CrCl	
Epzicom or Kivexa (abacavir/lamivudine)	1 tab PO QD	Substitute component drugs, adjusting dosage of each drug for CrCl	
Trizivir (zidovudine/abacavir/lamivudine)	1 tab PO BID	Substitute component drugs, adjusting dosage of each drug for CrCl	
Stribild (elvitegravir/cobicistat/tenofovir/emtricitabine)	1 tab PO QD	Do not initiate if CrCl <70 mg/mL; discontinue if CrCl <50 mg/mL	
Truvada (emtricitabine/tenofovir)	1 tab PO QD	CrCl (mL/min)	
		≥50	1 tablet QD
		30-49	1 tablet Q48H
		<30	Substitute component drugs, adjusting dosage of each drug for CrCl

Protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) do not appear to require dosage adjustment in persons with CKD. Some PIs and NNRTIs, however, do require changes in dosing strategy for patients on hemodialysis. (It should be noted that most PIs have not been studied in the setting of hemodialysis.) The CCR5 antagonist maraviroc should not be used for certain patients with CKD. Available recommendations for hemodialysis patients include the following:

Atazanavir

- Unboosted atazanavir should not be used.
- Treatment-naïve patients: atazanavir must be boosted by ritonavir.
- Treatment-experienced patients: atazanavir (boosted or unboosted) is not recommended.

Lopinavir/ritonavir

- QD dosing should not be used.
- In patients with PI resistance, lopinavir/ritonavir levels may be subtherapeutic.

Maraviroc

- CrCl <30 mL/min or on HD: not recommended with potent CYP3A inhibitors or inducers. Without potent CYP3A inhibitors or inducers: 300 mg BID (150 mg BID if postural hypotension occurs).

Nevirapine

- An additional dose (200 mg) should be given after each dialysis session.

Patient Education

- Early diagnosis of kidney disease is important. Acute kidney injury usually is reversible but may take time and may require temporary hemodialysis support.
- Advise patients to report all the medications they take, including over-the-counter medications and herbs or supplements.
- Risk factors for kidney disease are uncontrolled HIV infection (viral load above 4,000 copies/mL and CD4 count <200 cells/ μ L), coexisting conditions (diabetes mellitus, hypertension, hepatitis C), and ethnicity (African-Americans, Hispanic Americans, Asians, Pacific Islanders, and American Indians). Advise patients that it is important to reduce any modifiable risks, including optimizing HIV control and diabetes mellitus or hypertension management.
- Advise patients that control of blood pressure is important in slowing the progression of renal disease. Hypertension control can be maximized by both lifestyle modifications (e.g., weight lost, exercise, avoiding excessive alcohol intake) and antihypertensive medications. ACEIs or ARBs are the drugs of choice for patients with hypertension and kidney disease. Target blood pressure is <125/75 mm Hg for patients with proteinuric kidney disease.
- Educate patients that management of chronic kidney disease helps avoid or control complications such as high blood pressure, weak bones (osteodystrophy), anemia, and nerve damage (neuropathy).
- When the kidney disease progresses to end-stage renal disease, several options can be explored. These are dialysis, kidney transplant, or palliative care. There are two modes of dialysis, hemodialysis and peritoneal dialysis. A nephrologist and the patient can decide which option is best. HIV control (suppressed viral load, optimal CD4) is required if kidney transplant is to be considered.

Immune Reconstitution Inflammatory Syndrome

Background

For most patients, initiating antiretroviral therapy (ART) improves immune responses to a wide range of opportunistic pathogens. The process of ART-induced immune reconstitution typically is uneventful. However, a small percentage of patients develop inflammatory disease in response to specific opportunistic pathogens within a few weeks or months after initiating therapy. This exuberant inflammatory response has been called the immune reconstitution inflammatory syndrome (IRIS), also known as immune reconstitution syndrome (IRS) or immune reconstitution disease (IRD).

The term IRIS is used to describe two distinct entities:

- An exacerbation of a partially or successfully treated opportunistic infection (OI), referred to as paradoxical IRIS
- An inflammatory response to a previously undiagnosed (subclinical) OI, often more pronounced than the typical presentation of this OI, referred to as unmasking IRIS

IRIS may occur in response to many pathogens. IRIS commonly occurs in association with *Mycobacterium tuberculosis*, *Mycobacterium avium* complex (MAC), cytomegalovirus (CMV), and *Cryptococcus*, and it may occur with *Pneumocystis*, *Toxoplasma*, hepatitis B and C, human herpes virus 8 (HHV-8, which causes Kaposi sarcoma), and JC virus (which causes progressive multifocal leukoencephalopathy, PML).

Risk factors for development of paradoxical IRIS include low CD4 cell count (particularly <50 cells/ μ L) at time of ART initiation and high baseline HIV RNA. Starting ART in close proximity to initiation of treatment for a recognized OI also increases the risk of IRIS, though data also show that earlier ART initiation tends to reduce mortality and AIDS progression, particularly in persons with advanced immunosuppression (see “Timing of ART initiation,” below).

Paradoxical IRIS also can occur in the absence of ART, as has been reported during tuberculosis (TB) treatment. The specific mechanisms involved in the pathogenesis of IRIS are not well understood and may vary from one infection to another. However, experts believe that IRIS is caused by an enhanced and dysregulated immune response to disease-specific antigens, which leads to an overproduction of inflammatory mediators.

IRIS may be difficult to identify in clinical practice because the clinical presentation is nonspecific and, currently, there are no laboratory markers to identify the syndrome. To make the diagnosis of IRIS, the following must be excluded:

- Presence of a new OI or concomitant illness
- Failure of treatment for HIV infection (e.g., owing to poor adherence or drug resistance)
- Failure of treatment for a known OI (e.g., owing to drug resistance, inadequate treatment, or poor adherence)

The severity of IRIS varies widely, from mild to life-threatening. Treatment varies according to the specific pathogen and clinical situation, but typically includes continuing ART if possible, treating the OI as indicated, and adding antiinflammatory therapy (including corticosteroids) as needed.

Clinical Presentation

IRIS is largely a clinical diagnosis, and other conditions must be excluded, as indicated above. To consider IRIS in the differential diagnosis, clinicians must recognize the clinical findings (typical or atypical) of a specific OI and the temporal association with treatment (usually after ART initiation, but IRIS may occur with treatment of the OI alone). For example, for a patient with TB who has recently initiated ART after responding to treatment of TB, the “red flags” for a diagnosis of IRIS (rather than progression of the TB) would include new or worsening fever, new effusions, and new or worsening lymphadenopathy, in the absence of poor adherence to TB treatment or drug-resistant TB.

The clinical manifestations of IRIS associated with some common OIs are described below. (This is not an exhaustive list, but it includes most of the important IRIS manifestations seen in patients with HIV infection.)

Tuberculosis

The signs and symptoms of TB IRIS may include various clinical or radiologic features (e.g., new or worsening enlarged lymph nodes, fevers, weight loss, pulmonary symptoms, and radiographic features of TB such as infiltrates and pleural effusions). Nonpulmonary presentations may include expanding central nervous system (CNS) deficits or lesions, lymphadenopathy (mediastinal or peripheral), ascites, pericardial effusions, skin or visceral abscesses, bone lesions, and hypercalcemia. In a patient who is receiving therapy for active TB, the onset of TB IRIS typically occurs within weeks to several months after the patient begins ART and is more common among patients with low CD4 cell counts at the time of ART initiation (see chapter *Mycobacterium tuberculosis*).

Mycobacterium avium Complex

Lymphadenitis and fever are the characteristic symptoms of MAC IRIS, but pulmonary symptoms, abdominal pain, bone and hepatic involvement, and CNS manifestations may develop. Signs and symptoms of MAC IRIS may be clinically indistinguishable from active MAC. In contrast to disseminated MAC, MAC IRIS is associated with a rapid and striking increase in CD4 count (usually from <50 cells/ μL to ≥ 100 cells/ μL), and MAC bacteremia usually is absent. MAC IRIS can be mild and localized or it can be severe, requiring systemic antiinflammatory therapy (sometimes for long periods), in addition to anti-MAC therapy.

Cytomegalovirus

CMV IRIS is usually localized to the eye, as described below. However, CMV IRIS will rarely present with extraocular disease such as colitis, pancreatitis, or pneumonitis.

CMV retinitis

CMV retinitis may occur in patients with a history of CMV retinitis or in patients with no previous evidence of retinitis. In those with a previous diagnosis of CMV retinitis, a new opacified retinal lesion develops, frequently at the site of an earlier lesion. CMV retinitis IRIS is identical to active CMV retinitis on ophthalmologic examination. Clinical information, therefore, will guide the diagnosis, and patients should be monitored closely. As with other IRIS reactions, symptoms often are associated temporally with initiation of ART.

In order to initiate appropriate treatment, and to avoid IRIS, an ophthalmic examination to assess for the presence of CMV retinal infection should be performed for all patients with CD4 cell counts of <50 cells/ μL , preferably prior to the initiation of ART. This is particularly important for patients who report visual symptoms such as floaters or abnormal vision.

For patients who experience IRIS after being adequately treated for CMV retinitis, serial ophthalmologic examinations will reveal that the lesions clear without a new or different therapy for CMV. This clinical picture differs from that of retinal lesions caused by active CMV infection and uncontrolled CMV replication, in which lesions will increase in size or new lesions will appear, if appropriate CMV therapy has not been introduced (see chapter *Cytomegalovirus Disease*).

CMV vitreitis and CMV uveitis

CMV vitreitis and CMV uveitis are seen exclusively in patients with previous CMV retinitis infection who responded to ART.

CMV vitreitis

CMV vitreitis IRIS is an alarming syndrome, but a benign one. Patients who are receiving anti-CMV therapy typically present with acute onset of blurred vision and “floaters” caused by posterior segment inflammation. Ophthalmologic examination reveals numerous inflammatory cells in the vitreous humor. Symptoms usually resolve in 1 month without specific treatment and without any lasting visual effects.

CMV uveitis

In patients with a history of CMV retinitis, CMV uveitis IRIS may occur within months of ART initiation, but typically is a late complication, occurring about 3 years after patients begin ART. Uveitis is painless and primarily involves inflammation in the iris, the ciliary body, and the choroid layers. However, CMV uveitis may have serious sequelae. It often results in macular edema, epiretinal membrane formation, or cataracts, which can lead to permanent vision loss. Because of the risk of vision loss, clinicians should have a high index of suspicion for CMV uveitis.

Cryptococcal Meningitis

In patients with or without previously diagnosed cryptococcal meningitis, presentation of cryptococcal IRIS typically includes fever, headache, eye pain, and photophobia, and may include meningeal signs. In cryptococcal IRIS, analysis of cerebrospinal fluid (CSF) is characterized by high opening pressure and, unlike initial presentation of cryptococcal meningitis, an elevated white blood cell count and sterile fungal cultures. Onset has been reported between 1 week and 11 months after initiation of ART. Lymphadenitis, pulmonary disease, and cutaneous involvement also have been reported (see chapter *Cryptococcal Disease*).

Pneumocystis jiroveci Pneumonia

Pneumocystis jiroveci pneumonia (PCP) IRIS may occur in patients with current or recent PCP who are starting ART in the early weeks after initiation of PCP treatment. IRIS may present as worsening pulmonary symptoms (typically after corticosteroids given for the initial PCP treatment have been tapered or discontinued) and high fever in patients who had been improving on PCP therapy or in patients with recent successful treatment of PCP. Chest X-rays may show worsening lung involvement, and oxygen saturation or arterial blood gas measurements may show worsening hypoxia or alveolar-arterial oxygen gradient. PCP IRIS sometimes causes severe acute respiratory failure (see chapter *Pneumocystis Pneumonia*).

S: Subjective

Symptoms of IRIS will vary according to the specific illness.

Include the following in the history:

- Specific symptoms and time course of symptoms
- History of OIs, including recently diagnosed OIs
- Treatment of OIs, including date of initiation, medication adherence, duration of therapy, and clinical response
- ART initiation date, specific antiretroviral regimen, medication adherence, and previous history of ART
- CD4 cell count and HIV viral load before ART initiation
- Current CD4 cell count and HIV viral load, if known
- Other medications, especially new medications, including over-the-counter and herbal preparations

O: Objective

Obtain vital signs, including temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation.

Perform a thorough physical examination based on symptoms and suspicion of systems involved.

A: Assessment

In the appropriate clinical setting (especially in patients with advanced AIDS who recently initiated ART), IRIS should be considered in the differential diagnosis of patients who present with new or worsening symptoms. In these patients, the differential is broad, and causes other than IRIS should be considered carefully, including:

- Worsening or progression of a known OI despite treatment (e.g., owing to drug resistance or inadequate therapy)
- A new infection or illness
- Drug toxicity (e.g., hypersensitivity reaction)
- Failure of ART; progression of AIDS

Perform the appropriate diagnostic tests to exclude other etiologies. Consider consulting with an HIV specialist if the diagnosis is in question.

P: Plan

Diagnostic Evaluation

It is important to rule out new, incompletely treated, or untreated infections; malignancy; and other illnesses before concluding the patient has IRIS.

The workup of the patient with possible IRIS will depend on the specific clinical presentation. Perform laboratory tests, blood cultures, and other diagnostic tests as appropriate for the individual patient. These may include the following:

- Complete blood count (CBC) with differential, electrolytes and creatinine, liver function tests
- CD4 cell count and HIV viral load
- Blood cultures for bacteria, acid-fast bacteria (MAC), fungi
- Chest X-ray; other radiographic studies
- Sputum stain and culture

- Biopsy or culture of skin or other lesions
- Lumbar puncture and cerebrospinal fluid studies, if a CNS process is suspected
- Ophthalmologic examination
- Drug resistance testing for the OI being treated, if indicated

Treatment

Prevention and treatment recommendations from randomized prospective trials are lacking for most IRIS syndromes. However, the majority of cases of IRIS reported in the medical literature are not life-threatening and appear to have resolved within a matter of weeks to months with the following:

- Continuing the current ART regimen (unless the clinical presentation is life-threatening)
- Treating any newly identified, untreated OI
- If indicated, administering antiinflammatory medications to suppress the inflammatory process (prednisone was shown in one study to decrease hospital days and improve symptoms in TB IRIS in sub-Saharan Africa; anecdotal data support the use of nonsteroidal antiinflammatory drugs in mild-to-moderate IRIS)

For patients with recent OIs that resolved with a full course of appropriate therapy, it is not always necessary to resume antimicrobial therapy or to change maintenance therapy. For example, if a patient with TB IRIS has finished a full course of treatment for TB, repeat treatment is not indicated, once recurrent TB infection has been ruled out. If a patient with previously treated cryptococcal meningitis is receiving maintenance therapy and IRIS develops, the therapy does not need to be altered. However, if IRIS reveals a new, untreated OI, that infection should be treated appropriately. For instance, if new cryptococcal meningitis presents as IRIS, the cryptococcus should be treated as indicated. If treatment is in question, consult with an HIV specialist.

Timing of ART initiation

The risk of IRIS is highest for patients who start ART with low CD4 counts (<50 - 100 cells/ μL) and those for whom ART is initiated soon after OI treatment is begun. The optimal time for ART initiation in the setting of some OIs is not known, but increasing evidence, including from randomized controlled trials, suggests a mortality benefit to early ART initiation in patients with a variety of newly diagnosed OIs. For patients with TB and HIV infection, for example, data from three randomized studies show reductions in mortality and/or AIDS progression with early initiation of ART, though the urgency of ART varied with CD4 count: for those with CD4 counts of <50 cells/ μL , benefit was seen if ART was initiated within 2 weeks of TB treatment start (compared with delaying until week 8-12 of TB treatment). For those with CD4 counts of 50 - 200 cells/ μL , data support ART initiation between 2 weeks and 2 months after the start of TB treatment. ART should not be deferred until after TB treatment for any patient, regardless of the CD4 cell count. In TB meningitis, however, the optimal ART start time is not clear; in one study, immediate ART increased the risk severe adverse effects and death. In cryptococcal meningitis, data about timing of ART initiation are conflicting; many experts advise delaying ART until 2-10 weeks after the start of cryptococcus treatment.

Decisions about the timing of ART initiation may depend on a number of variables, including the specific pathogen, the severity of the OI, whether the CNS is involved (IRIS in the CNS may be life-threatening), the medication burden, and the potential for drug toxicity or drug interactions. In most cases, ART initiation should be considered within 1-2 weeks after initiation of OI therapy, particularly in patients with TB and CD4 counts of <50 cells/ μL . For patients with TB meningitis, cryptococcal meningitis, or other CNS or ocular infections, many specialists

would recommend delaying ART until they have received appropriate OI treatment for at least 2 weeks. For decisions about initiating ART in patients with active OIs, consult with an HIV specialist.

IRIS in resource-limited settings

As access to ART improves in resource-limited countries, IRIS increasingly is being recognized in patients receiving ART. Clinicians should include IRIS in the differential diagnosis when evaluating patients who recently have begun ART and present with new or worsening symptoms of an OI. However, limited diagnostic testing resources may make it difficult to establish IRIS and other diagnoses.

Given that coinfection with HIV and TB is epidemic in many countries, and because IRIS is not uncommon in patients with TB, clinicians should be particularly vigilant about symptoms that may signal IRIS. As in resource-sufficient countries, consultation with a clinician trained in caring for patients with HIV is recommended if diagnosis or treatment is in question.

Patient Education

- Patients starting ART who have CD4 counts of <100 cells/ μ L or known concomitant OIs should be counseled about the likelihood of IRIS.
- All patients starting ART should be advised to contact the clinic promptly if they experience new or worsening symptoms.
- Advise patients to take their medications for HIV and for the treatment or prevention of OIs exactly as prescribed.

Anal Dysplasia

Background

Anal cancer is a squamous cell cancer associated with human papillomavirus (HPV), the same virus that is associated with cervical cancer (see chapter *Cervical Dysplasia*). The anal canal and cervical canal share a common embryologic origin: both have a squamocolumnar transition zone and are prone to infection with HPV, a sexually transmitted virus. HPV infection, in combination with cofactors, may stimulate dysplastic changes in the cervix or anus that may develop through precursor stages into squamous cell cancer. In the United States, the incidence of anal cancer in the general population is approximately 1:100,000 per year. In HIV-infected men and women, the incidence of anal cancer and the prevalence of its precursors are significantly higher than in the general population. Advanced immunosuppression, as demonstrated by lower CD4 cell counts, appears to increase the risk of anal intraepithelial neoplasia (AIN), a precursor to cancer, and anal cancer.

Rates of anal cancer also are higher among men who have sex with men (MSM), whether HIV infected or uninfected, compared with the general population. Current rates in an HIV-infected MSM population have been estimated to be as high as 70-144 per 100,000. Although most studies have examined anal dysplasia and cancer in MSM, its prevalence also is high among HIV-infected women and heterosexual men. Some studies of HIV-infected individuals have shown that anal HPV infection is present in 93% of MSM and 76% of women, and that anal dysplasia (any grade) is present in 56% of MSM and 26% of women. In some studies of HIV-infected women, anal dysplasia has been seen more frequently than cervical dysplasia, and it has not been exclusive to those with behavioral risk factors (e.g., history of receptive anal intercourse). HIV-infected heterosexual men with no history of receptive anal intercourse also have elevated risks of anal HPV infection. Thus, although receptive anal intercourse may increase the likelihood of anal HPV infection, it is not a prerequisite for anal HPV or dysplasia.

Screening strategies for anal dysplasia and cancer and the optimal management of abnormal test results are areas in which questions remain unanswered. The rationale for screening for anal cancer and its precursors is based on the success of cervical Papanicolaou (Pap) screening in reducing cervical cancer incidence and mortality. Because of the similarities between cervical and anal dysplasia, many experts postulate that many of the paradigms of managing cervical cytologic abnormalities may be translated to management of anal dysplasia. However, there are no randomized clinical trials that document the value of screening for anal precancers.

Current guidelines from the HIV Medicine Association of the Infectious Diseases Society of America recommend anal pap tests for MSM, women with a history of abnormal cervical Pap tests or a history of anal receptive sex, and all HIV-infected persons with genital warts, though they do not specify screening intervals. The New York State Department of Health AIDS Institute recommends that an anal Pap test be done at baseline and annually thereafter for MSM, patients with a history of anogenital warts, and women with abnormal cervical or vulvar histology, and many HIV clinics elsewhere do routine screening. Further investigations are ongoing to define appropriate screening intervals, diagnostic approaches, indications for therapy, and modalities of treatment.

ART and subsequent immune reconstitution does not appear to alter the prevalence or distribution of anal cancers and anorectal disease nor does it appear to reduce the progression of AIN and other cancer precursors.

For information on prevention of HPV infection, see "Prevention," below.

S: Subjective

Patients with anal dysplasia usually are asymptomatic, and the condition cannot be identified without screening tests. Exophytic anal condylomata may cause itching, discomfort, or bleeding, but are usually associated with low-risk phenotypes of HPV and low-grade dysplasia (note, however, that oncogenic HPV types also may be present). Anal cancer may cause nonspecific symptoms such as pain (with defecation or after intercourse), itching, bleeding, or sensation of a rectal mass.

Risk factors for anal dysplasia and cancers include the following:

- HIV infection
- CD4 count of <200 cells/ μ L
- RAI
- HPV infection
- Genital warts (or history of genital warts)
- Immunosuppression
- High-grade cervical or vulvar dysplasia
- Cigarette smoking
- Multiple sex partners

Ask patients about these risk factors, about previous history of anal dysplasia or cancer, and about previous screening.

O: Objective

Examine the genital and perianal region, and perform a digital anorectal examination. Look and feel for masses, condylomata, and other abnormalities such as hypo- or hyperpigmented plaques or lesions, and lesions that bleed. Note that simple visual examination may not reveal abnormalities. In women, also examine the vulva, vagina, and cervix. Examine the inguinal lymph nodes.

If the digital examination is performed in conjunction with an anal Pap test, the Pap specimen should be obtained before the

introduction of lubrication.

Anoscopic examination with the naked eye may not reveal any abnormality because dysplastic tissue tends to be flat and difficult to differentiate from normal anal tissue; application of 3% acetic acid is required (see below for a description of how high-resolution anoscopy [HRA] is performed).

A: Assessment

HIV-infected individuals with anal dysplasia have an increased risk of progression to anal cancer. If the history or physical examination reveals abnormalities suggestive of anal dysplasia or anal cancer, an appropriate evaluation should be undertaken. Because most patients with anal dysplasia have no symptoms, anal cancer screening using a Pap test can be considered if follow-up evaluation of an abnormal cytologic result (ASCUS or higher, see Bethesda 2001 grading system, below) by high-resolution anoscopy is available either on-site or by referral.

P: Plan **Screening**

As mentioned above, some organizations and many experts recommend that anal Pap tests and digital anal examination be part of the initial evaluation of both male and female HIV-infected patients. The intervals for screening have not been established, but (based on recommendations for cervical cancer screening) if the first test result is normal, the anal Pap usually is repeated in approximately 6 months. If both results are normal, then anal Pap tests can be performed annually. Some clinicians would consider more frequent screening in patients with genital warts, cervical dysplasia, or a history of treatment for anal dysplasia. Any patients with positive results should be referred for further evaluation; see below.

An anal Pap test is done using a standard Pap

kit. The swab or cytobrush should be inserted into the anal canal, past the anorectal junction, and withdrawn while rotating it against the anal walls to collect cells. The sample should then be handled according to the kit manufacturer's instructions. (See "References," below, for information about a video on how to conduct an anal Pap screen that is available from the Johns Hopkins University Local Performance Site of the Pennsylvania/MidAtlantic AIDS Education and Training Center.)

As with cervical cytology, anal cytology is graded using the Bethesda 2001 system, which categorizes disease in increasing order of severity as follows:

- Negative for intraepithelial lesion or malignancy
- Atypical squamous cells of undetermined significance (ASCUS)
- Atypical squamous cells – cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade squamous intraepithelial lesion (HSIL)
- Squamous cell carcinoma (SCC)

Other abnormalities, such as atypical glandular cells (AGC), may be noted.

All individuals with abnormal anal cytology, defined as ASCUS or higher, should be referred for HRA and biopsy to grade the lesion. HRA typically is performed at specialty anal cancer practices or clinics, colorectal surgery and gastrointestinal specialty facilities, and some academic medical centers.

There currently are no recommendations concerning HPV testing of anal specimens.

Evaluation of Cytologic Abnormalities

HRA of the anal canal should be performed using a colonoscope for magnification (16x) and the application of 3% acetic acid with or without Lugol iodine solution to aid in visualization of dysplastic lesions. Abnormal

areas should be examined by biopsy.

Anoscopic features of high-grade disease are similar to those seen in the cervix; these include coarse punctation, mosaicism, and the presence of ring glands.

Treatment

The goal of treatment is to prevent progression to anal cancer. Treatment of HSIL to prevent anal cancer is biologically plausible, following the model of cervical dysplasia treatment. However, the indications for treatment of anal dysplasia, the efficacy of treatment, and the most effective treatments have not been optimally defined.

The focus of treatment is on high-grade, premalignant AIN. Patients should be referred to an anal dysplasia specialist specialty clinic, if possible. Specific treatment may vary depending on the size, location, extent of the lesions, and histological grade. Therapies include topical 5-fluorouracil, cryotherapy, infrared coagulation, laser therapy, and surgical excision. Infrared coagulation, an in-office procedure, has been shown to be effective in treating HIV-infected patients with high-grade dysplasia. With some therapies, treatment-associated pain and other complications may occur, and recurrence of dysplastic lesions is common.

LSIL is not considered premalignant, but it frequently progresses to high-grade dysplasia. Some specialists do not treat LSIL but monitor regularly instead with HRA, whereas others choose to treat LSIL to prevent progression.

Prevention

Prevention of HPV infection can be challenging. Latex or plastic barriers may block transmission of HPV in areas covered by these barriers and their use is recommended to prevent transmission or acquisition of HPV (as well as HIV and other sexually transmitted diseases). However, infection may occur through bodily contact outside the area covered by the barriers.

A quadrivalent HPV vaccine against certain oncogenic (types 16 and 18) and wart-causing (types 6 and 11) types of HPV is FDA approved for prevention of anal dysplasia and anal cancer caused by the covered types in males and females 9-26 years of age, and for prevention of genital warts, its use is recommended. (The quadrivalent vaccine also is approved for prevention of cervical cancer and cervical, vaginal, and vulvar dysplasia). A second vaccine against HPV types 16 and 18 has been approved for females (see chapter *Cervical Dysplasia*).

The vaccine is not effective against HPV types other than those covered by the vaccine, and it may not be protective against a covered type to which a patient has been exposed previously. For optimal protection, the vaccine should be given before the individual is exposed to HPV through sexual activity. It is likely to be less effective in older adolescents and adults who may already have been infected with one or more of the covered HPV types. There are few data on the use of the vaccines in persons older than 26 years, and they are not approved for this group. Importantly, vaccination does not offer perfect protection from all oncogenic HPV viruses, so consideration should be given to screening individuals who have been vaccinated in the same way as unvaccinated individuals, as described above.

Patient Education

- All HIV-infected men and women should be encouraged to use condoms during vaginal, anal, and oral sex to prevent the spread of HPV. However, condoms do not offer complete protection from HPV.
- All patients should be counseled on how to reduce or avoid unprotected anal receptive intercourse.
- Both women and men who are HIV infected have an increased risk of developing anal dysplasia and cancer. MSM are at higher risk than other men of developing anal dysplasia.
- Emphasize the importance of keeping follow-up appointments to allow for early detection of precancerous lesions, further grading of abnormalities by HRA, and appropriate monitoring and treatment of abnormalities.
- Patients who have anal dysplasia should be informed about anal cancer symptoms, such as new-onset anal pain, bleeding, or the development of a mass. Patients should call their health care provider if these symptoms develop.
- If an anal Pap test is to be performed, advise patients to avoid having anal sex, douching, or using enemas before the test.

Candidiasis, Oral and Esophageal

Background

Oropharyngeal candidiasis (“thrush”), a fungal disease of the oral mucosa and tongue, is the most common intraoral lesion among persons infected with HIV. In the absence of other known causes of immunosuppression, oral thrush in an adult is highly suggestive of HIV infection. Although thrush in the absence of esophageal disease is not an AIDS-defining condition, it usually occurs with CD4 counts of <200 cells/ μL . Three clinical presentations of thrush are common in people with HIV: pseudomembranous, erythematous, and angular cheilitis. *Candida* also may infect the esophagus in the form of esophageal candidiasis, which causes dysphagia (difficulty with swallowing) or odynophagia (pain with swallowing). Esophageal candidiasis is an AIDS-defining condition, generally occurring in individuals with CD4 counts of <200 cells/ μL . It is the most common cause of esophageal infection in persons with AIDS.

Oropharyngeal and esophageal candidiasis are caused most commonly by *Candida albicans*, although non-*albicans* species increasingly may cause disease and may be resistant to first-line therapies.

S: Subjective

Oropharyngeal Candidiasis

The patient may complain of painless white patches on the tongue and oral mucosa, smooth red areas on the dorsal tongue, burning or painful areas in the mouth, a bad or unusual taste, sensitivity to spicy foods, or decreased appetite.

Esophageal Candidiasis

The patient complains of difficulty or pain with swallowing, or the sensation that food is “sticking” in the retrosternal chest. Weight loss is common, and nausea and vomiting may occur. Fever is not common with candidal esophagitis and suggests another cause. The patient may note symptoms of oral candidiasis (as above).

O: Objective

Perform a thorough oropharyngeal examination. Patients presenting with oral candidiasis may be totally asymptomatic, so it is important to inspect the oral cavity thoroughly. Patients with esophageal

candidiasis usually have oral thrush and often experience weight loss.

Lesions can occur anywhere on the hard and soft palates, under the tongue, on the buccal mucosa or gums, or in the posterior pharynx.

Pseudomembranous oral candidiasis appears as creamy white, curdlike plaques on the buccal mucosa, tongue, and other mucosal surfaces. Typically, the plaques can be wiped away, leaving a red or bleeding underlying surface. Lesions may be as small as 1-2 mm, or they may form extensive plaques that cover the entire hard palate.

Erythematous oral candidiasis presents as one or more flat, red, subtle lesions on the dorsal surface of the tongue or the hard or soft palate. The dorsum of the tongue may show loss of filiform papillae.

Angular cheilitis causes fissuring and redness at one or both corners of the mouth and may appear alone or in conjunction with another form of oral *Candida* infection.

A: Assessment

A partial differential diagnosis for the two conditions is as follows:

Oropharyngeal Candidiasis

- Oral hairy leukoplakia
- Abrasion of the mucosa or a topical burn
- Bacterial gingivitis
- Periodontitis

Esophageal Candidiasis

- GERD
- Cytomegalovirus (CMV)
- Herpes simplex virus (HSV)
- Aphthous ulceration

P: Plan

Diagnostic Evaluation

Oropharyngeal candidiasis

Clinical examination alone usually is diagnostic. If the diagnosis is unclear, organisms may be detected on smear or culture if necessary.

- On a potassium hydroxide (KOH) preparation of a smear collected by gentle scraping of the affected area with a wooden tongue depressor, visible hyphae or blastospores on KOH mount indicate *Candida* infection.
- Culture is diagnostic and may detect non-*albicans* species in cases resistant to first-line therapies. Sensitivities also may be needed in such cases to diagnose azole-resistant infections.

Esophageal candidiasis

A presumptive diagnosis usually can be made with a recent onset of typical symptoms, especially in the presence of thrush, and empiric antifungal therapy may be started as a diagnostic trial. If the patient fails to improve clinically after 3-7 days of therapy, endoscopy should be performed for a definitive diagnosis.

Treatment

Treatment of oropharyngeal candidiasis

- Oral therapy is convenient and very effective as first-line treatment. Note that azole antifungal drugs are not recommended for use during pregnancy. Topical therapy is less expensive, safe for use during pregnancy, and effective for mild to moderate disease. All therapies should be given for 7-14 days.
- Preferred oral therapy: Fluconazole 100 mg PO QD
- Preferred topical therapy:
 - Clotrimazole troches 10 mg dissolved in the mouth 5 times daily
 - Miconazole mucoadhesive tablet 50 mg PO QD
- Alternative oral therapy:
 - Itraconazole oral solution 200 mg PO QD
 - Posaconazole oral solution 400 mg PO BID for 1 day, then 400 mg PO QD (Note: These agents may present a greater risk of drug interactions (see “Potential ARV Interactions,” below) and hepatotoxicity than do fluconazole or topical treatments)
- Alternative topical therapy: Nystatin oral suspension 4-6 mL “swish and swallow” QID or 1-2 pastilles 4-5 times daily

Treatment of esophageal candidiasis

- Duration of therapy: 14-21 days
- Preferred therapy:
 - Fluconazole 100 mg PO (up to 400 mg) QD; IV therapy can be given if the patient is unable to swallow pills.
 - Itraconazole oral solution 200 mg PO QD
- Alternative therapy:
 - Voriconazole 200 mg PO or IV BID
 - Posaconazole 400 mg PO BID
 - IV therapy with an echinocandin

(caspofungin, micafungin, anidulafungin), or amphotericin, if the patient is unable to tolerate PO therapy (Note: Treatment with echinocandins is associated with a higher rate of relapse; see “Potential ARV Interactions,” below, regarding potential drug-drug interactions between voriconazole or posaconazole and ARVs)

Treatment of refractory candidiasis

Oral or esophageal candidiasis that does not improve after at least 7-14 days of appropriate antifungal therapy can be considered refractory to treatment. The primary risk factors for development of refractory candidiasis are CD4 counts of <50 cells/ μ L and prolonged, chronic antifungal therapy (especially with azoles). In such cases, it is important to confirm the diagnosis of candidiasis. As noted, other infections such as HSV, CMV, and aphthous ulcerations can cause similar symptoms. Once refractory candidiasis is confirmed, several treatment options are available, including the following:

- Posaconazole 400 mg PO BID
- Itraconazole oral solution \geq 200 mg PO QD
- Voriconazole 200 mg PO or IV BID (see “Potential ARV Interactions,” below)
- Therapy with an echinocandin (caspofungin 50 mg QD; micafungin 150 mg QD; anidulafungin 100 mg for 1 dose, then 50 mg QD), or amphotericin B deoxycholate or lipid preparation
(Note: Treatment with echinocandins is associated with a higher rate of relapse. See “Potential ARV Interactions,” below, for information on potential drug interactions.)

The choice of treatment depends upon anticipated drug-drug interactions, the patient’s preferences and tolerability, availability of medications, and the provider’s experience. Consult with an HIV or infectious disease expert for advice about treatment regimens.

Maintenance therapy

Use caution when considering chronic maintenance therapy, because it has been associated with refractory and azole-resistant candidiasis, as noted above. Fluconazole 100 mg PO QD or TIW can be effective for patients who have had multiple or severe recurrences of oral disease (azole sensitive). Fluconazole 100-200 mg PO QD or posaconazole 400 mg PO BID (see “Potential ARV Interactions,” below) can be considered for patients who have had frequent or severe recurrent esophageal candidiasis.

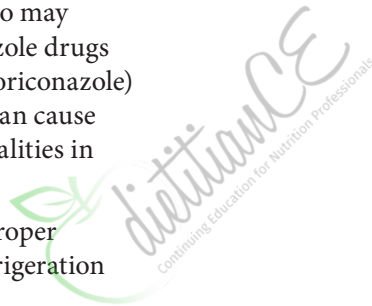
There are no data to guide this decision; it is reasonable to discontinue maintenance therapy in patients who achieve immunologic responses on fully suppressive ART (i.e., with an increase in CD4 count to \geq 200 cells/ μ L). Patients with fluconazole-refractory oropharyngeal or esophageal disease who respond to IV echinocandins are recommended to take posaconazole or voriconazole suppression until they achieve immune reconstitution on ART, because of high relapse rates.

Potential ARV Interactions

There may be significant drug-drug interactions between certain systemic antifungals (particularly itraconazole, voriconazole, and posaconazole) and ritonavir-boosted protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), elvitegravir/cobicistat, or maraviroc. Some combinations are contraindicated and others require dosage adjustment of the ARV, the antifungal, or both. Check for adverse drug interactions before prescribing. For example, voriconazole use is not recommended for patients taking ritonavir-boosted PIs, and dosage adjustment of both voriconazole and NNRTIs may be required when voriconazole is used concurrently with NNRTIs. See relevant tables in the U.S. Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, or consult with an expert.

Patient Education

- Patients should maintain good oral hygiene by brushing teeth after each meal.
- A soft toothbrush should be used to avoid mouth trauma.
- Advise patients to rinse the mouth of all food before using lozenges or liquid medications.
- Tell patients to avoid foods or liquids that are very hot in temperature or very spicy.
- Patients who have candidiasis under a denture or partial denture should remove the prosthesis before using topical agents such as clotrimazole or nystatin. When not in use, the prosthesis should be stored in a chlorhexidine solution.
- Pregnant women and women who may become pregnant should avoid azole drugs (e.g., fluconazole, itraconazole, voriconazole) during pregnancy because they can cause skeletal and craniofacial abnormalities in infants.
- Patients should be informed of proper storage of oral solutions (e.g., refrigeration requirements).



Candidiasis, Vulvovaginal

Background

Vulvovaginal candidiasis is a yeast infection caused by several types of *Candida*, typically *Candida albicans*. This disease is common in all women, but may occur more frequently and more severely in immunocompromised women.

Although refractory vaginal *Candida* infections by themselves should not be considered indicators of HIV infection, they may be the first clinical manifestation of HIV infection and can occur early in the course of disease (at CD4 counts of >500 cells/ μ L). The frequency of vaginal candidiasis tends to increase as CD4 counts decrease; however, this may be attributable in part to increased use of antibiotics among women with advanced HIV infection.

Risk factors for candidiasis include diabetes mellitus and the use of oral contraceptives, corticosteroids, or antibiotics.

S: Subjective

The patient may complain of itching, burning, or swelling of the labia and vulva; a thick white or yellowish vaginal discharge; painful intercourse; and pain and burning on urination.

The most important elements in the history include the following:

- Type and duration of symptoms
- Previous vaginal yeast infection
- Oral contraceptive use
- Recent or ongoing broad-spectrum antibiotic therapy
- Recent corticosteroid therapy
- Sexual exposures (to evaluate for sexually transmitted diseases)
- Diabetes history
- Cushing syndrome
- Obesity
- Hypothyroidism
- Pregnancy
- Use of douches, vaginal deodorants, or bath additives

O: Objective

Perform a focused physical examination of the external genitalia, vagina, and cervix. This may reveal inflammation of the vulva with evidence of discharge on the labial folds and vaginal opening. Speculum examination usually reveals a thick, white discharge with plaques adhering to the vaginal walls and cervix. Bimanual examination should not elicit pain or tenderness and otherwise should be normal.

A: Assessment

Rule out other causes of vaginal discharge and pruritus:

- Bacterial vaginosis
- Atrophic vaginitis
- Chemical or mechanical causes
- Trichomoniasis
- Gonorrhea, chlamydia, and other sexually transmitted diseases
- Scabies
- Pediculosis

P: Plan

Diagnostic Evaluation

A presumptive diagnosis is made on the basis of the clinical presentation and potassium hydroxide (KOH) preparation:

- Perform microscopic examination of a KOH preparation of vaginal secretions. This usually reveals pseudohyphae and *Candida* spores (presumptive diagnosis).
- Definitive diagnosis rarely is needed, but may be made by analysis of a culture of vaginal secretions; this may be useful if azole-resistant or non-*albicans* species are suspected.
- In the presence of urinary tract symptoms (beyond external vulvar burning), perform urinalysis, culture, or both on a clean-catch urine specimen.
- Consider testing for gonorrhea and chlamydia in patients with a history of possible sexual exposure.

Treatment

Uncomplicated infections

Topical medications

- Prescribe topical vaginal antifungal agents in the form of cream or suppositories, including the following: butoconazole, clotrimazole, miconazole, nystatin, terconazole, and tioconazole. Treat for 3-7 days and offer refills depending on the time to the next scheduled clinic visit. The creams also may be used on the vulva for treatment of pruritus.

Note that the mineral-oil base in topical vaginal antifungal preparations may erode the latex in condoms, diaphragms, and dental dams. Advise the patient to use alternative methods to prevent HIV transmission or conception, or to discontinue intercourse while using these medications. Nonlatex condoms (plastic and polyethylene only) or “female” condoms (polyurethane) can be used.

Oral medications

Preferred

- Fluconazole 150 mg PO, single dose (see “Treatment notes,” below)

Alternative

- Itraconazole oral solution 200 mg PO QD for 3-7 days (see “Treatment notes,” below)

Complicated infections

Severe or recurrent candidiasis

Severe or recurrent candidiasis is defined as four or more episodes within 1 year. Consider the following treatments:

- Fluconazole 100-200 mg PO QD for ≥ 7 days (see Treatment notes,” below)
- Topical therapy as described above, for ≥ 7 days

For severe cases that recur repeatedly, secondary prophylaxis can be considered (e.g., fluconazole 150 mg PO once weekly).

Treatment notes

- Systemic azole drugs should not be used during pregnancy, and women taking azoles should use effective contraception. Topical azoles are recommended for the treatment of pregnant women.
- Resistance to azole medications may develop, especially with prolonged use of oral agents.
- Avoid ketoconazole: Case reports have associated ketoconazole with a risk of fulminant hepatitis (1 in 12,000 courses of treatment with oral ketoconazole). Experts agree that the risks may outweigh the benefits for women with vulvovaginal candidiasis. Ketoconazole interacts with many other drugs, including some antiretroviral drugs.

Potential ARV Interactions

There may be significant drug-drug interactions between certain systemic antifungals (particularly itraconazole, voriconazole, and posaconazole) and ritonavir-boosted protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), elvitegravir/cobicistat, or maraviroc. Some combinations are contraindicated and others require dosage adjustment of the ARV, the antifungal, or both. Check for adverse drug interactions before prescribing. For example, voriconazole use is not recommended for patients taking ritonavir-boosted PIs, and dosage adjustment of both voriconazole and NNRTIs may be required when voriconazole is used concurrently with NNRTIs. See relevant tables in the U.S. Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, or consult with an expert.

- Women who continue to have symptoms can purchase miconazole (e.g., Monistat) or clotrimazole (e.g., Gyne-Lotrimin) vaginal cream over the counter. Advise patients to start using these as soon as symptoms return and to contact the clinic if symptoms worsen while they are taking these medicines.
- Women taking oral fluconazole, ketoconazole, or other azoles must avoid pregnancy. Some birth defects have been reported.
- The mineral-oil base in topical vaginal antifungal preparations may erode the latex in condoms, diaphragms, and dental dams. Advise patients to use alternative methods to prevent HIV transmission or conception or to discontinue intercourse while using these medications. Nonlatex condoms (plastic and polyethylene only) or “female” condoms (polyurethane) can be used.
- Sex toys, douche nozzles, diaphragms, cervical caps, and other items can reinfect patients if not properly cleaned and thoroughly dried after use.
- Some studies have suggested that eating yogurt with live cultures (check labels) can reduce the occurrence of vaginal yeast infections.

Patient Education

- Advise patients to wash external genitals daily with a fresh washcloth or water-soaked cotton balls and to wipe the vulva and perirectal area from front to back after toileting. Women should not use baby wipes on inflamed vulval tissue because they may increase irritation.
- Women should avoid the use of perfumed soaps, bubble baths, feminine hygiene or vaginal deodorant products, and bath powders.
- Advise women not to douche.
- Women should wear cotton underwear and avoid tight, constrictive clothing, particularly pantyhose.
- If patients are prescribed medication for vaginal candidiasis, they should take the medication exactly as prescribed and finish the medicine even during a menstrual period.

Cervical Dysplasia

Background

Precancerous lesions and cancer of the cervix are associated with human papillomavirus (HPV), a sexually transmitted virus. Carcinogenic strains of HPV, in conjunction with other factors, may cause dysplasia and cancer not only of the cervix, but also of the vulva, vagina, anus, and oropharynx. HIV-infected women have a higher prevalence of HPV infection than do HIV-uninfected women, and a higher prevalence of oncogenic HPV types. They are about 10 times more likely to develop cervical dysplasia, or intraepithelial neoplasia (CIN), precursors to cervical cancer. Unfortunately, they also have a higher risk of invasive cervical cancer and tend to have more aggressive forms of cervical cancer and poorer responses to treatment. Invasive cervical cancer is an AIDS-defining illness.

The risk of high-grade cervical lesions and cervical cancer appears to be higher for women with advanced immunodeficiency than for women with preserved CD4 cell counts. Other risk factors for dysplasia and cervical cancer include African-American ethnicity, a history of smoking, younger age at onset of sexual intercourse, and multiple sex partners. Effective antiretroviral therapy (ART) with immune reconstitution has not been shown to prevent the progression of CIN.

Screening for cervical cancer and appropriate intervention in women with high-grade CIN (CIN 3) are effective in preventing cervical cancer. Frequent monitoring and careful follow-up in women with low-grade lesions are essential for preventing progression to invasive disease. For all HIV-infected women (if they have had sex partners), including adolescents and young women, Papanicolaou (Pap) testing should be performed routinely. An initial test should be done at the time of HIV diagnosis, repeated 6 months after the first test, then performed annually thereafter if the results are normal. (See chapter *Initial and Interim Laboratory and Other Tests*.)

Because the risk of anal dysplasia also is increased among HIV-infected women (in some studies, rates of anal dysplasia were higher than rates of cervical dysplasia), many experts and some guidelines recommend concurrent screening for anal dysplasia. For further information, see chapter *Anal Dysplasia*.

For information on prevention of HPV infection, see "Prevention," below.

HRSA HAB Performance Measures

Percentage of female patients with a diagnosis of HIV who have a **Pap screening** in the measurement year

(Adult and Adolescent measure)

S: Subjective

Patients with CIN or early cervical cancer usually are asymptomatic, and disease will not be diagnosed unless screening is performed. Genital condylomata (warts) indicate infection with HPV and typically are associated with low-risk types of HPV; however, a mixture of HPV types may be present, and women with genital warts may have concurrent dysplasia.

The classic symptom of early invasive cervical neoplasia is intermittent, painless bleeding between menstrual periods, which may present initially as postcoital spotting. Late symptoms of invasive cervical carcinoma include flank and leg pain, dysuria, hematuria, rectal bleeding, and obstipation.

Ask all female patients about risk factors for, previous history of, and preventive measures against cervical dysplasia and cancer, including the following:

- Genital warts; previous or current HPV infection
- Previous abnormal cervical Pap test result
- Previous abnormal anal Pap test result
- Previous cervical cancer; when and how treated
- Sexual activity before age 20
- History of multiple sex partners
- Cigarette smoking
- CD4 count of <200 cells/ μ L
- Pregnancy
- Oral contraceptive use
- History of HPV vaccination

O: Objective

Perform a focused examination of the abdomen and pelvis. Examine the external genital and perianal region. Perform speculum and bimanual examinations to evaluate the vagina and cervix. Look for lesions, masses, warts, and cervical inflammation or discharge, as well as exophytic or ulcerative cervical lesions with or without bleeding. Note that simple visual examination may not reveal abnormalities.

A: Assessment

HIV-infected women have an increased risk of cervical dysplasia with progression to cervical cancer. If abnormalities of cervical disease are suspected, an appropriate evaluation should be performed. Because most women with CIN have no symptoms, routine screening should be performed for all women.

P: Plan

Screening

Perform Pap screening for all HIV-infected women. The initial test should be conducted at the time of HIV diagnosis, a second (if the first is normal) should be performed 6 months later. Screening should be repeated annually thereafter throughout life if all results are normal. (For HIV-uninfected adolescents and young women, recent guidelines recommend beginning cervical screening at age 21; for HIV-infected young women, guidelines suggest screening beginning within 1 year of first sexual activity, given the risk of progression of cervical abnormalities.) If a Pap result is abnormal, see below. Also consider screening for anal dysplasia with an anal Pap test (see chapter *Anal Dysplasia*).

Cervical (and anal) cytology usually is graded using the Bethesda 2001 system (see “References,” below), which categorizes disease in increasing order of severity as follows:

- Negative for intraepithelial lesion or malignancy
- Atypical squamous cells of undetermined significance (ASCUS)
- Atypical squamous cells, cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade squamous intraepithelial lesion (HSIL)
- Squamous cell carcinoma (SCC)

Other abnormalities may be noted, including the following:

- Atypical glandular cells (AGCs), including the following subcategories:
 - AGC not otherwise specified (AGC NOS) (includes endocervical, endometrial, or glandular cells)
 - AGC, favor neoplasia (includes endometrial or glandular cells)
 - AIS (endocervical adenocarcinoma in situ)
- Infectious organisms such as *Trichomonas*

Evaluation of Cytologic Abnormalities

Atypical squamous cells of undetermined significance

If ASCUS is present without inflammation or suspected neoplastic process, several options for management exist.

- Most experts recommend that all women with ASCUS be referred for colposcopy and directed biopsy, regardless of their degree of immunodeficiency. If the biopsy result shows no dysplasia (and the examination is adequate), the patient should be monitored by annual Pap tests.
- As an alternative, patients who are considered reliable for follow-up may repeat the Pap test in 6-12 months. If repeat Pap is reported at greater than ASCUS, the woman should be referred for colposcopy.
- There are limited and conflicting data to support the use of HPV DNA testing as part of the management of HIV-infected women with ASCUS. Current OI guidelines (see "References," below) emphasize that HPV testing alone is not recommended.

Atypical squamous cells, cannot exclude HSIL

Women with abnormalities suggestive of high-grade dysplasia should be referred for colposcopy.

Low-grade squamous intraepithelial lesion

Women with LSIL should be referred for colposcopy and directed biopsy.

High-grade squamous intraepithelial lesion or squamous cell carcinoma

Women with HSIL are at high risk of high-grade intraepithelial neoplasia or cervical cancer and should undergo colposcopy with endocervical assessment and directed biopsy as soon as possible. Refer to an oncology specialist for treatment.

Atypical glandular cells

Because of the high rate of significant lesions in patients with AGS, colposcopy with endocervical sampling is recommended for all subcategories, including AIS. In women over age 35, endometrial sampling is recommended in addition to colposcopy and endocervical sampling. Refer to an appropriate specialist for evaluation.

Treatment

The optimal management of precancerous cervical lesions has not been identified clearly for all classes of CIN. Consult with an HIV-experienced gynecologist, oncologist, or other dysplasia specialist. High-grade lesions in women with satisfactory colposcopy are typically treated with ablation (e.g., cryotherapy, electrocautery, laser vaporization) or excision (e.g., loop electrosurgical excision [LEEP], laser or cold-knife conization). For women with unsatisfactory colposcopy, excisional methods are recommended.

Prevention

Latex or plastic barriers may block transmission of HPV in areas covered by these barriers and have been shown to reduce the risk of infection with oncogenic HPV. Although infection may occur through bodily contact outside the area covered by the barriers, the use of condoms is recommended to prevent transmission or acquisition of HPV (as well as HIV and other STDs).

Two vaccines have been approved by the U.S. Food and Drug Administration for the prevention of certain HPV strains; these are recommended for HIV-infected women and girls 9-26 years of age. They have been shown to reduce rates of cervical dysplasia; the quadrivalent vaccine also has been shown to protect against vulvar, vaginal, and anal dysplasia (as well as anogenital warts) related to the covered HPV types.

- **Quadrivalent** (Gardasil): includes HPV types 16 and 18 (which cause nearly 70% of cervical cancer, as well as vaginal, vulvar, and anal cancer), and types 6 and 11 (which cause most anogenital warts)
- **Bivalent** (Cervarix): includes HPV types 16 and 18

The quadrivalent vaccine also is recommended for use with males aged 9-26 for prevention of genital warts and anal intraepithelial neoplasia.

These vaccines are not effective against HPV types other than those covered by the vaccine, and they may not be protective against a covered type to which a patient has been exposed previously. For optimal protection, these vaccines should be given before the individual is exposed to HPV through sexual activity. They are likely to be less effective in older adolescents and adults who already may have been infected with one or more of the covered HPV types. There are few data on the use of the vaccines in persons older than 26, and they are not approved for this group. Importantly, women who have been vaccinated should continue to be screened for cervical cancer as described above; vaccination does not protect women perfectly from all oncogenic HPV viruses.

Patient Education

- Recommend the use of latex or polyurethane male or female condoms for vaginal or anal intercourse and plastic or latex barriers for oral sex to reduce the risk of transmitting HPV (the usual cause of cervical cancer) to partners. Barriers also reduce the risk of exposure to other sexually transmitted pathogens.
- Patients who smoke should be advised to quit. Cigarette smoking appears to heighten the risk of cervical cancer and makes HPV more difficult to treat. Discuss options for smoking cessation (see chapter *Smoking Cessation*), and refer patients to the American Lung Association if local programs are available.
- Emphasize the importance of keeping follow-up appointments for Pap screening or colposcopy to allow early detection of precancerous lesions and appropriate monitoring of abnormalities.

- For women with dysplasia who require treatment, emphasize that early treatment is essential for managing the disease and preventing the development of cancer. Advise patients to keep all medical appointments.



Cryptococcal Disease

Background

Cryptococcosis usually presents as a systemic or central nervous system (CNS) fungal infection caused by the yeast *Cryptococcus neoformans*. The organism is ubiquitous, and is particularly plentiful in soils enriched with bird droppings. It also may be present in fruit skins or juices, and in unpasteurized milk. In immunocompetent patients, cryptococcal infection usually is asymptomatic, self-limited, and confined to the lungs. In persons with advanced HIV infection (e.g., those with CD4 counts of <100 cells/ μ L), *Cryptococcus* may cause life-threatening illness, either from a new exposure or through reactivation of a previously acquired latent infection.

In HIV-infected patients, *Cryptococcus* can infect almost all organs in the body, but most commonly causes meningitis or meningoencephalitis. Disseminated disease, pneumonia, and skin lesions also may be seen.

S: Subjective

Symptoms depend upon the locus of infection. In the case of meningitis, the patient typically experiences subacute onset of fever, headaches, and malaise, which worsen over the course of several weeks. These symptoms may be accompanied by nausea with or without vomiting. Classic meningeal signs, nuchal rigidity, and photophobia are present in only about 25% of cases. Cryptococcal meningitis may cause confusion, personality or behavior changes, blindness, deafness, and, if left untreated, coma and death. If the disease involves the lungs, patients may experience cough or shortness of breath, pleuritic chest pain, and fever. Skin lesions may be present.

O: Objective

Perform a thorough physical examination with particular attention to the following:

- Vital signs, hydration status
- Funduscopic findings
- Neck (for nuchal rigidity, which is uncommon)

- Lungs, especially if respiratory symptoms are present
- Neurologic evaluation, including cranial nerves, visual acuity, and mental status
- Skin

Cryptococcal Meningitis

Physical examination may reveal papilledema with loss of visual acuity and cranial nerve deficits (particularly in cranial nerves III and VI).

Cryptococcal Pulmonary Disease

Examination may reveal tachypnea or fine rales.

Cutaneous Infection

Skin lesions are variable and may appear as papules, nodules, or ulcers; they often resemble molluscum lesions.

A: Assessment

The differential diagnosis for cryptococcal meningitis or meningoencephalitis is broad and includes other infectious causes of meningitis (fungal, mycobacterial, bacterial, viral), syphilis, lymphoma, mass lesions, intoxication, HIV encephalopathy, and trauma. (See chapter *Neurologic Symptoms*.)

The differential diagnosis for cryptococcal pneumonia is broad and includes other infectious causes of pneumonia (fungal, mycobacterial, bacterial, viral), malignancy, and congestive heart failure. (See chapter *Pulmonary Symptoms*.)

P: Plan

Diagnostic Evaluation

The workup should include serum cryptococcal antigen (CrAg), which usually is very sensitive, and blood cultures, including bacterial, acid-fast bacilli (AFB), and fungal cultures. Patients with symptoms of disseminated or pulmonary infection should be evaluated by chest X-ray (which may show diffuse or focal infiltrates, sometimes appearing as nodular or miliary; intrathoracic adenopathy; or pleural effusions), sputum culture (including fungal and AFB cultures), and AFB stain. Bronchoscopy and bronchoalveolar lavage may be necessary for diagnosis. For cutaneous lesions, consider biopsy and histopathologic evaluation or culture. As part of the general fever workup, urinalysis and urine cultures should be checked.

Patients with a positive serum CrAg, another positive test for *Cryptococcus*, or signs or symptoms of meningitis should undergo analysis of the cerebrospinal fluid (CSF). If neurologic symptoms or signs are present, obtain a computed tomography (CT) scan of the brain before performing a lumbar puncture (LP) to rule out a mass lesion or increased intracranial pressure (ICP), which could cause herniation upon LP. Always measure the CSF opening pressure; a high ICP contributes to morbidity and mortality and determines the need for serial LP to manage the increased ICP. Send the CSF for the following:

- CrAg (usually positive at high titer in meningitis)
- Fungal culture
- India ink stain (less sensitive than CSF CrAg; perform if CSF CrAg is not available)

- Cell count
- Glucose
- Protein

For exclusion of other etiologies, perform CSF Venereal Disease Research Laboratory (VDRL) test, bacterial culture, AFB smear and culture, or polymerase chain reaction (PCR), if tuberculosis is suspected, and other tests as indicated by the patient's symptoms and exposures.

Treatment

Cryptococcal meningitis

Acute treatment of cryptococcal meningitis consists of two phases: induction and consolidation. Acute treatment is followed by chronic maintenance (suppressive) therapy.

Induction

Patients with cryptococcal meningitis should be hospitalized to start at least 2 weeks of induction therapy.

Preferred therapy:

- Liposomal amphotericin B 3-4 mg/kg IV QD + flucytosine 25 mg/kg PO QID

Lipid formulations of amphotericin B are less nephrotoxic than amphotericin B deoxycholate and appear to be equally effective.

Amphotericin-based therapy, in combination with flucytosine, is recommended. If these are not available, are contraindicated, or are not tolerated by the patient, the other indicated induction therapies may be considered.

Alternative therapy:

- Amphotericin B lipid complex 5 mg/kg IV QD + flucytosine 25 mg/kg PO QID
- Amphotericin B deoxycholate 0.7-1.0 mg/kg IV QD + flucytosine 25 mg/kg PO QID
- Liposomal amphotericin B 3-4 mg/kg IV QD + fluconazole 800 mg PO or IV QD
- Amphotericin B deoxycholate 0.7-1.0 mg/kg IV QD + fluconazole 800 mg PO or IV QD
- Liposomal amphotericin B 3-4 mg/kg IV QD alone
- Fluconazole 400-800 mg PO or IV QD + flucytosine 25 mg/kg PO QID
- Fluconazole 1,200 mg PO or IV QD alone

The primary alternative to amphotericin-based therapy is high-dose fluconazole (800-1,200 mg PO QD), with or without flucytosine. Among the newer antifungal agents, echinocandins have no activity against *Cryptococcus*. Voriconazole and posaconazole have good in vitro activity and may be considered for treatment of relapsed disease but not as first-line agents. The efficacy of alternative regimens is not well defined. See "Potential ARV Interactions," below, regarding drug-drug interactions between these antifungals and ARVs.

Amphotericin B causes many adverse effects, including fever, rigors, hypotension, nausea, nephrotoxicity and electrolyte disturbances, anemia, and leukopenia. The patient's hemoglobin, white blood cell (WBC) count, platelets, electrolytes, magnesium, and creatinine must be monitored closely during treatment. Liposomal forms of amphotericin cause fewer adverse effects. These should be used particularly for patients who have difficulty tolerating standard amphotericin B and for those who are at high risk of renal failure. Electrolytes and creatinine should be monitored. Flucytosine is associated with bone marrow and liver toxicity, and complete blood counts and liver function tests

should be monitored during induction therapy. If available, flucytosine levels can be evaluated 3-5 days after the start of therapy, with a target 2-hour post-dose level of 30-80 mg/mL; a level of >100 mg/mL should be avoided. Note that the dosage of flucytosine must be adjusted for patients with renal insufficiency.

Resistance testing may be considered for patients who have relapsed and for those for whom fluconazole failed to sterilize the CSF.

Consolidation

After clinical improvement with 2 weeks of induction therapy, and a negative CSF culture on repeat LP, treatment can be switched to fluconazole (400 mg PO QD for at least 8 weeks). Itraconazole (200 mg PO BID) is an alternative for patients who cannot take fluconazole. It should be noted that itraconazole is less effective than fluconazole and has significant drug interactions with commonly used medications.

Maintenance

After completing acute treatment, the patient should receive chronic maintenance therapy with fluconazole (200 mg PO QD) to prevent recurrence of cryptococcosis.

Maintenance therapy should be continued for life, unless the patient has completed induction and consolidation therapy followed by at least 1 year of maintenance therapy, and has sustained CD4 cell recovery in response to effective antiretroviral therapy (ART) (CD4 count ≥ 100 cells/ μ L for at least 3 months during ART). Maintenance therapy should be restarted if the CD4 count declines to <100 cells/ μ L.

Management of elevated ICP

Elevated ICP significantly increases the morbidity and mortality of cryptococcal meningitis and should be treated by the removal of CSF. The CSF opening pressure should be checked on the initial LP. If the initial opening pressure is >250 mm H₂O,

remove up to 30 mL of CSF to lower the ICP by 50%, if possible. LP and CSF removal should be repeated daily as needed for ICP reduction. A lumbar drain or ventriculoperitoneal shunt may be needed if the initial opening pressure is >400 mm H₂O, or in refractory cases. There is no role for acetazolamide, mannitol, or steroids in the treatment of elevated ICP.

A repeat LP is not required for patients who did not have elevated ICP at baseline and are responding to treatment. If new symptoms develop, a repeat LP is indicated. Serum CrAg titers are not useful in monitoring response to treatment.

Cryptococcal pulmonary disease, with negative CSF CrAg and culture results

After CSF cryptococcal disease has been excluded, treat with fluconazole if symptoms are mild or moderate and chest imaging shows focal infiltrates: 400 mg PO QD for 12 months, then 200 mg QD for maintenance. Otherwise, consider amphotericin induction, as described above with CNS disease. Maintenance therapy should be continued for life, unless the patient has sustained CD4 cell recovery in response to effective ART (CD4 count of ≥100 cells/μL for at least 6 months during ART) and with a minimum of 12 months of antifungal therapy. Therapy should be restarted if the CD4 count declines to <100 cells/μL.

Cutaneous infection, with negative CSF CrAg and culture results

Treat with fluconazole 400 mg PO QD for 6-12 months, then continue with 200 mg QD for chronic maintenance therapy, as discussed above.

Asymptomatic antigenemia

Data are limited for management of asymptomatic antigenemia, which can be associated with development of subsequent disease. Fungal cultures of CSF and blood should be obtained; if either result is positive for cryptococcal growth, treatment should be initiated for symptomatic meningoencephalitis or disseminated disease. If no

meningoencephalitis is found, fluconazole 400 mg PO QD should be given until immune reconstitution occurs; treatment may be discontinued per maintenance guidelines described above.

Cryptococcus IRIS

Immune reconstitution through ART is effective for preventing recurrence of cryptococcal infections. However, initiating ART within the first 1-2 months after starting treatment for cryptococcal infection may result in worsening or recurrence of symptoms because of immune reconstitution inflammatory syndrome (IRIS). IRIS can be life-threatening in cryptococcal meningeal disease. IRIS and relapse of cryptococcal disease (e.g., treatment failure) must be differentiated; in IRIS, the serum and CSF cultures are negative. (See chapter *Immune Reconstitution Inflammatory Syndrome*.)

Optimal timing of ART initiation in cryptococcal CNS disease is not known. Some experts recommend treating severe cryptococcosis with effective antifungal therapy for 2-10 weeks before starting ART, to decrease the risk of IRIS. On the other hand, if the CD4 count is very low (e.g., <50 copies/μL), it is important to initiate ART as soon as possible.

Other treatment notes

Pregnancy

Fluconazole and other azole drugs should be avoided during the first trimester of pregnancy, and voriconazole and posaconazole should be avoided throughout pregnancy. During the first and second trimesters, pregnant women should be treated with amphotericin for both induction and consolidation therapy. Flucytosine is teratogenic at high doses in rats and is classified as a pregnancy class C drug; it should be used during pregnancy only if the benefits clearly outweigh the risks.

Preventive therapy

Studies have suggested that routine primary prophylaxis for cryptococcal disease in patients with CD4 counts of <100 cells/ μ L is effective at preventing cryptococcal infection but is not cost efficient. Therefore, it is not routinely recommended.

Potential ARV Interactions

There may be significant drug-drug interactions between certain systemic antifungals, (particularly itraconazole, voriconazole, and posaconazole) and ritonavir-boosted protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), elvitegravir/cobicistat, or maraviroc. Some combinations are contraindicated and others require dosage adjustment of the ARV, the antifungal, or both. Check for adverse drug interactions before prescribing. For example, voriconazole use is not recommended for patients taking ritonavir-boosted PIs, and dosage adjustment of both voriconazole and NNRTIs may be required when voriconazole is used concurrently with NNRTIs. See relevant tables in the U.S. Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, or consult with an expert.

Patient Education

- Cryptococcosis is not curable in persons with low CD4 cell counts and may require lifelong treatment. Patients should be instructed to take their treatment without interruptions.
- Even with therapy, disease may recur. Patients should report fevers or recurrence of other symptoms immediately.
- Antiretroviral therapy and improvement in immune system health are essential for prevention of recurrence.
- Patients should avoid pregnancy while taking any oral antifungal drug. Fetal craniofacial and skeletal abnormalities have been reported.

Cryptosporidiosis

Background

Cryptosporidiosis is caused by a species of protozoan parasite that typically infects the mucosa of the small intestine, causing watery diarrhea. Diarrhea may be accompanied by nausea, vomiting, abdominal cramping, and occasionally fever. The infection is spread by the fecal-oral route, usually via contaminated water, and is highly contagious. The course of infection depends on the immune status of the host. In immunocompetent individuals, cryptosporidiosis usually is self-limited and can cause a mild diarrheal illness. However, in HIV-infected patients with advanced immunosuppression, cryptosporidiosis can cause severe chronic diarrhea, electrolyte disturbances, malabsorption, and profound weight loss. Infection also can occur outside the intestinal tract and can cause cholangitis, pancreatitis, and hepatitis. In severe cases, cryptosporidiosis can be life-threatening without aggressive fluid, electrolyte, and nutritional support. Patients at greatest risk of acquiring cryptosporidiosis are those with CD4 counts of <100 cells/ μL . Immune reconstitution inflammatory syndrome (IRIS) has not been described in association with cryptosporidiosis.

S: Subjective

The patient may complain of some or all of the following: watery diarrhea (can be profuse), abdominal pain or cramping, flatulence, nausea, vomiting, anorexia, fever, and weight loss.

The history should include questions about the presence and characteristics of the symptoms listed above, as well as the following:

- Stool frequency (typically 6-26 bowel movements daily)
- Stool volume (up to 10 liters per day and can be described as “cholera-like” in some patients with AIDS)
- Duration of symptoms (subacute or acute onset)
- Associated symptoms
- Exposures: recent travel to areas with unsafe water supply; ingestion of possibly contaminated water while swimming, boating, or camping; oral-anal contact, fecal exposures during sexual contact
- Recent CD4 cell count (highest risk is in patients with CD4 counts of <100 cells/ μL)

O: Objective

Perform a thorough physical examination with particular attention to the following:

- Vital signs
- Hydration status (e.g., orthostatic vital signs, mucous membrane moistness, skin turgor)
- Weight (compare with previous values; document weight loss)
- Signs of malnourishment (e.g., cachexia, wasting, thinning hair, pallor)
- Abdominal examination for bowel sounds (usually hyperactive), tenderness (can be diffuse), rebound
- Recent CD4 count

A: Assessment

In HIV-infected patients with advanced immunosuppression, the differential diagnosis includes other infectious causes of subacute or chronic diarrhea or cholangitis, such as microsporidia, *Isospora*, *Giardia*, cytomegalovirus (CMV), and *Mycobacterium avium* complex (MAC), as well as lymphoma.

P: Plan

Diagnostic Evaluation

- Test the stool for ova and parasites, including *Cryptosporidium*. Diagnosis is made by microscopic identification of the *Cryptosporidium* oocysts in stool.
- Be sure to ask the laboratory to look for *Cryptosporidium*; certain labs do not look for these parasites or their precursor, the oocyst, unless requested.
- Test for fecal leukocytes. The result usually is negative in cryptosporidiosis; if positive, consider the possibility of a second enteric infection, especially if the CD4 count is low, or a different infection.
- Among persons with profuse diarrhea, a single stool specimen usually is adequate for diagnosis. For patients with milder disease, repeat stool sampling may be needed.
- If stool is negative for ova and parasites, consider a referral for biopsy of the gastrointestinal mucosa or flexible sigmoidoscopy.
- If cholangitis is suspected, consider abdominal ultrasound to look for biliary ductal dilatation, and endoscopic retrograde cholangiopancreatography (ERCP).
- Check electrolytes; conduct liver function studies including alkaline phosphatase and bilirubin to check for possible biliary or hepatic infection.
- If fever is present, obtain blood cultures.
- Conduct other diagnostic testing as indicated by the history and physical examination (e.g., evaluation for CMV, MAC, and other infectious causes of diarrhea or cholangitis) (see chapter *Diarrhea*).

Treatment

Preferred Strategy:

- Effective antiretroviral therapy (ART) with immune reconstitution (and CD4 count of >100 cells/ μ L) can resolve cryptosporidiosis, and it is the primary treatment. All patients with cryptosporidiosis should be initiated on ART (see chapter *Antiretroviral Therapy*). Patients who are on incompletely suppressive ART should have their regimens optimized.
- Provide supportive care and symptomatic relief (this may require hospitalization in cases of severe dehydration), including the following:
 - Aggressive fluid and electrolyte replacement as needed
 - Oral rehydration (solutions containing glucose, sodium bicarbonate, potassium, magnesium, and phosphorus); in severe cases, IV hydration may be required
 - Antidiarrheal agents: atropine/diphenoxylate (Lomotil), loperamide (Imodium), tincture of opium (Paregoric)
 - Antispasmodics
 - Antiemetics
 - Topical treatment for the anorectal area, as needed (witch hazel pads [e.g., Tucks]), sitz baths)

Alternative Management Strategies:

- No antiparasitic therapy has been proven to consistently and effectively cure cryptosporidiosis if used without ART. Use of nitazoxanide and paromomycin can be considered. They should be given in conjunction with ART, but never instead of ART; symptomatic treatment and hydration also should be given, as above.
- Nitazoxanide is approved for treatment of diarrhea caused by *Cryptosporidium parvum*, the most common strain of *Cryptosporidium*. It may increase the likelihood of clinical response.

- Usual adult dosage: 500-1,000 mg PO BID for 14 days
- Adverse events associated with nitazoxanide are limited and typically mild; there are no important drug-drug interactions
- Paromomycin 50 mg QID for 14-21 days

For patients with weight loss, nutritional supplementation is a critical aspect of treatment. In some cases, partial or total parenteral nutrition may be necessary while patients are awaiting clinical improvement in response to ART or other therapies. Consult or refer to a dietitian or nutritionist, if available. If not, assess food intake and counsel the patient about increasing caloric and nutritional intake.

Cryptosporidiosis in Resource-Limited Settings

Cryptosporidium infection in HIV-uninfected populations is more common in countries with overcrowding and poor sanitary conditions. The disease also is associated with rainy seasons and is frequent among children <2 years of age.

The prognosis for HIV-infected patients with cryptosporidiosis who lack access to ART is poor. In one study, the mean survival time of coinfecting patients was 25 weeks.

Prevention of Disease and Exposure

- Effective ART with maintenance or restoration of adequate immune function will prevent severe cryptosporidiosis.
- Scrupulous handwashing can prevent the spread of cryptosporidiosis, and HIV-infected patients should be advised to wash their hands after potential contact with human feces (diapering small children, handling pets, gardening, and before and after sex).
- HIV-infected patients should avoid sexual practices that could lead to direct (e.g., oral-anal) or indirect (e.g., penile-anal) contact with feces and should be advised to use barrier methods during sex (e.g., condoms

and dental dams).

- HIV-infected persons should avoid drinking water from lakes or rivers. Waterborne infection also can result from recreational activities such as boating, fishing, and swimming.
- HIV-infected patients should avoid raw oysters as the cryptosporidial oocysts can survive in oysters for >2 months.
- Rifabutin and clarithromycin, when taken for MAC prophylaxis, appear to reduce the risk of cryptosporidiosis. However, current data are insufficient to recommend their use as prophylaxis against cryptosporidiosis.

Patient Education

- Recommend scrupulous handwashing for the patient and all contacts, especially household members and sex partners.
- Explain that effective ART is the best treatment for alleviating symptoms and helping the immune system eradicate the parasite.
- Advise the patient to increase fluid intake (not alcohol), and avoid foods that aggravate diarrhea. A lactose-free diet may improve symptoms.
- Educate the patient about healthful food choices that increase caloric intake and nutrition.
- Provide supportive counseling; discuss how to manage symptoms and the isolation that may accompany chronic diarrhea.

Cytomegalovirus Disease

Background

Although chronic infection with cytomegalovirus (CMV) rarely causes disease among immunocompetent persons, it is a major cause of morbidity and mortality in HIV-infected patients with CD4 counts of <50 cells/ μL . CMV infection causes disease in several organ systems, including the central nervous system (CNS) (chorioretinitis, encephalitis, polyradiculopathy, myelopathy) and the gastrointestinal (GI) tract (oral ulcers, esophagitis, hepatitis, colitis, intestinal perforation), as well as life-threatening adrenalitis and pneumonitis. The prevalence of chronic infection with CMV, a member of the human herpesvirus family, is high among sexually active adults (40-60% in resource-rich countries and 80-90% in resource-poor countries). CMV is spread by sexual or other types of close personal contact, blood-to-blood contact (via transfusion or needle sharing), organ transplantation, and perinatal transmission. As with other herpesviruses, CMV is not cleared from the body, but is kept in a state of latency by an intact immune system. Symptomatic disease represents either primary infection or reactivation of latent infection that has escaped immunologic control. Effective antiretroviral therapy (ART) greatly reduces the risk of CMV reactivation and disease.

Immune reconstitution inflammatory syndrome

Although effective ART greatly reduces the risk of CMV reactivation and disease, patients on effective ART may experience CMV-related visual changes.

- Patients without a previous history of CMV disease will occasionally present with full-blown CMV retinitis after starting ART. This is thought to reflect delayed restoration of CMV-specific immunity. It is diagnosed and treated in an identical manner as for patients diagnosed with CMV disease who are not taking effective ART.
- Approximately 20% of patients with previously treated CMV retinitis may experience CMV-related immune reconstitution uveitis (IRU) after starting successful ART. Symptoms include floaters and moderate, occasionally severe, vision loss. The most common causes of vision loss are posterior disease, specifically cystoid macular edema (CME) and epiretinal membrane (ERM) formation, although inflammation of the anterior region and cataract formation also can occur. It is not clear whether treatment with steroids or anti-CMV antivirals is effective. (See chapter *Immune Reconstitution Inflammatory Syndrome*.)

S: Subjective

The patient may present with symptoms involving various organ systems, including the following:

• CNS, including the eye:

- Floaters, scotomata (blind spots), “flashing lights,” loss of peripheral or field vision (chorioretinitis)
- Headache, difficulty concentrating, sleepiness, personality changes (encephalitis, dementia)

- Bilateral lower extremity weakness, urinary retention, incontinence, spasticity (polyradiculopathy)
- Low-back pain, especially radiating to the perianal area (polyradiculopathy, myelitis)
- Family members or caregivers may report confusion, apathy, lethargy, somnolence, withdrawal, or personality changes in the patient (CMV encephalitis, dementia)

- **GI tract disease:**

- Mouth ulcerations
- Dysphagia or odynophagia (esophagitis)
- Abdominal pain and bloody diarrhea, weight loss, rectal ulcers, fever (colitis)

- **Disease outside the CNS or GI tract:**

- Persistent fever, fatigue, weight loss (adrenalitis)
- Shortness of breath, dyspnea on exertion, dry cough (pneumonia; rare in patients with advanced HIV infection)
- Pancytopenia (bone marrow infection)

The history should include questions about the presence and characteristics of the symptoms listed above, as well as the following:

- Duration of symptoms
- Associated symptoms
- Recent CD4 count; nadir CD4 count (risk is highest when count is <50 cells/ μ L)
- Whether the patient is taking ART; if so, date initiated, specific medications, and CD4 and HIV RNA responses

O: Objective

Perform a thorough physical examination with particular attention to the following:

- **Vital signs:** Document fever.
- **Weight:** Compare with previous values; document weight loss.
- **Eyes:** Funduscopic examination in patients with CMV retinitis may show pathognomonic “cottage cheese in ketchup” yellow-white lesions, representing vascular hemorrhages and exudates.
- **Nervous system:** Evaluate mental status and perform a complete neurologic examination, including cranial nerves, sensation (sensory deficits may occur with preserved vibratory sense and proprioception), motor, deep tendon reflexes, coordination, and gait.

A: Assessment

For HIV-infected patients with advanced immunosuppression, the differential diagnosis includes the following:

- For suspected CMV retinitis: consider cotton-wool spots, HIV retinopathy, and progressive outer or acute retinal necrosis.
- For suspected CMV encephalitis: consider other causes of neurologic deterioration such as progressive multifocal leukoencephalopathy, toxoplasmosis, CNS lymphoma, and other mass lesions.
- For suspected CMV enteritis: consider gastrointestinal pathogens such as *Mycobacterium avium* complex, *Cryptosporidium*, other parasites, and lymphoma.
- For suspected CMV pneumonitis: consider *Pneumocystis jiroveci* and other respiratory pathogens.

P: Plan

Diagnostic Evaluation

CMV can be detected by serology, culture, antigen testing, nucleic acid amplification, or examination of tissue samples. However, serologic tests are not reliable for diagnosing CMV disease because most adults are seropositive and because patients with advanced AIDS may serorevert while remaining infected. Furthermore, for HIV-infected patients, demonstration of CMV in the blood, urine, semen, cervical secretions, or bronchoalveolar lavage (BAL) fluid does not necessarily indicate active disease, although patients with end-organ disease usually are viremic.

Diagnosis of end-organ disease generally requires demonstration of tissue invasion. The recommended evaluation is as follows:

CMV retinitis

Dilated retinal examination should be performed emergently by an ophthalmologist experienced in the diagnosis of CMV retinitis. The diagnosis usually is based on the identification of typical lesions. Diagnosis and monitoring should include serial examinations with photography to assess and follow response to treatment and to detect failure to respond early enough to change therapy. If the diagnosis is uncertain, aqueous or vitreous fluid samples can be sent for polymerase chain reaction (PCR) evaluation for CMV and other possible infectious agents.

Other sites

Detection of CMV at other sites requires visualization of typical lesions (e.g., on endoscopy or BAL) and tissue biopsy. Viral inclusions (“owl’s eye cells”) in tissue biopsy samples demonstrate invasive disease (as opposed to colonization). **Because retinitis is the most common manifestation of CMV disease, patients with CNS, gastrointestinal, or pulmonary disease should undergo ophthalmologic evaluation to detect subclinical retinal disease.**

Neurologic CMV disease

- **Encephalitis:** Magnetic resonance imaging (MRI) of the brain should be done to rule out mass lesions. CMV effects may appear as periventricular or meningeal enhancement. Lumbar puncture should be performed; cerebrospinal fluid (CSF) should be analyzed for CMV (by PCR, which is sensitive and specific), cell count (may show lymphocytic or mixed lymphocytic or polymorphonuclear pleocytosis), glucose (may be low), and protein (may be high). A brain biopsy may be performed if the diagnosis is uncertain after imaging and CSF evaluation.

- **Polyradiculopathy:** Spinal MRI should be done to rule out mass lesions. In CMV disease, nerve root thickening may be present. Lumbar puncture with CSF analysis should be performed, as described above.
- **Myelitis:** Spinal MRI should be done to rule out mass lesions. Cord enhancement may be present. Lumbar puncture with CSF analysis should be performed, as described above.

Gastrointestinal CMV disease (esophagitis or colitis)

- Perform endoscopy with visualization of ulcers and obtain tissue biopsy to look for inclusion bodies.

Pulmonary CMV disease

- Perform chest radiography showing interstitial pneumonia and obtain lung biopsy to look for inclusion bodies.

Treatment

Valganciclovir, ganciclovir, foscarnet, and cidofovir may be effective for treating CMV end-organ disease. The choice of therapy depends on the site and severity of the infection, the level of underlying immunosuppression, the patient’s ability to tolerate the medications and adhere to the treatment regimen, and the potential medication interactions.

Immune reconstitution through ART is a key component of CMV treatment and relapse prevention. CMV flares may occur if patients develop immune reconstitution inflammatory syndrome (see chapter *Immune Reconstitution Inflammatory Syndrome*). Although decisions about the timing of ART should be individualized, in most cases of CMV end-organ disease, ART probably should not be delayed for more than 2 weeks after starting treatment for CMV.

CMV retinitis

Treatment consists of two phases: initial therapy and chronic maintenance therapy.

Initial therapy

For patients with sight-threatening (zone 1) disease, the preferred treatment strategy is a combination of intravitreal and systemic therapy. Intravitreal therapy delivers high doses of drug to the retina immediately. Ganciclovir intraocular implants are no longer available, but patients may be treated with intravitreal injections of ganciclovir or foscarnet.

In the past, about half of patients treated with only local therapy (specifically, ganciclovir implants) developed disease in the contralateral eye, and one third experienced systemic disease within 3 months of implantation. Therefore, patients who receive intravitreal therapy also should be treated systemically with valganciclovir or an alternative therapy as below.

For patients with peripheral retinitis (beyond zone 1), systemic therapy alone may be given. Oral valganciclovir (see below) is the preferred treatment because it is easy to administer and is not associated with the surgery- or catheter-related complications seen with intraocular treatments and IV therapies. This formulation quickly converts to ganciclovir in the body and has good bioavailability. Valganciclovir should be used only if the patient is thought to be capable of strict adherence. Other possible IV treatments include ganciclovir, ganciclovir followed by oral valganciclovir, foscarnet, and cidofovir. See below for dosing recommendations.

For sight-threatening disease:

- Intravitreal injection of ganciclovir (2 mg/injection or foscarnet (2.4 mg/injection) 1-4 doses over the course of 7-10 days **plus** systemic therapy as below

Preferred systemic therapy:

- Valganciclovir 900 mg PO BID for 14-21 days, then QD

Alternative systemic therapy:

- Ganciclovir 5 mg/kg IV Q12H for 14-21 days, then QD
- Ganciclovir 5 mg/kg IV Q12H for 14-21 days, then valganciclovir 900 mg PO QD
- Foscarnet 60 mg/kg IV Q8H or 90 mg/kg Q12H for 14-21 days, then 90 mg/kg Q24H
- Cidofovir IV 5 mg/kg weekly for 2 weeks, then every other week (must be given with probenecid [2 g PO 3 hours before, 1 g PO 2 hours after, and 1 g PO 8 hours after the cidofovir infusion] and IV saline to decrease the risk of renal toxicity)

For peripheral lesions:

- Systemic therapy as above

Note: Valganciclovir, ganciclovir, and foscarnet require dosage adjustment in patients with renal insufficiency. Cidofovir is contraindicated for use by patients with renal insufficiency or proteinuria.

Monitor patients closely to gauge the response to therapy. Repeat the dilated retinal examination after completion of induction therapy, 1 month after initiation of therapy, and monthly during anti-CMV therapy, with photography to document progression or resolution of disease. Consult with a specialist if the response to therapy is suboptimal.

Note: Retinal detachment may occur in up to 50-60% of patients in the first year after diagnosis. Regular follow-up with an ophthalmologist is required for all patients. Patients should be instructed to report any vision loss immediately.

Chronic maintenance therapy

After initial CMV treatment, lifelong maintenance therapy should be given to prevent recurrence, and patients need regular reevaluation by an ophthalmologist. Select the specific treatment in consultation with an ophthalmologist.

Preferred therapy:

- Valganciclovir 900 mg PO QD

Alternative therapy:

- Ganciclovir 5 mg/kg IV 5-7 times per week
- Foscarnet 90-120 mg/kg IV QD
- Cidofovir 5 mg/kg IV every other week (administer with probenecid and IV hydration, as above)

Discontinuation of maintenance therapy can be considered for patients with inactive CMV and sustained immune reconstitution on ART (CD4 count of >100 cells/ μ L for at least 3-6 months). However, the decision should be guided by factors such as the extent and location of the CMV lesions and the status of the patient's vision. An ophthalmologist who is experienced in caring for HIV-infected patients with CMV should be involved in making any decision to discontinue therapy, and patients should receive regular ophthalmologic follow-up. Maintenance therapy should be resumed if the CD4 count drops to <100 cells/ μ L or the patient develops other signs of HIV progression.

Neurologic CMV disease

The optimal treatment for neurologic disease has not been determined. Prompt initiation of dual therapy with IV ganciclovir and foscarnet may be effective for some patients. Chronic maintenance therapy usually is not recommended for patients who recover and are on effective ART, unless the disease recurs.

Gastrointestinal and pulmonary CMV disease

CMV colitis and esophagitis are usually treated with IV ganciclovir or foscarnet for 21-42 days, until symptoms have resolved. Treatment should be changed to valganciclovir (900 mg QD) when the patient is able to absorb oral medications. In mild cases in which patients are able to tolerate and absorb it, valganciclovir may be used from the beginning (refer to the dosing recommendations above).

Some specialists recommend a follow-up endoscopy to verify regression of lesions before discontinuing therapy.

For pulmonary CMV infections, optimal therapy has not been defined. IV ganciclovir or foscarnet is recommended. The efficacy of valganciclovir has not been determined.

Many experts do not recommend maintenance therapy for gastrointestinal or pulmonary CMV infections for patients whose CMV symptoms resolve and who are on effective ART.

Immune reconstitution inflammatory syndrome retinitis or uveitis

Urgent consultation with experts is recommended. Corticosteroids may be beneficial.

Monitoring CMV therapies

The medications used to treat CMV have several important potential adverse effects, and monitoring for these is required. Valganciclovir and ganciclovir have been associated with bone marrow suppression, neutropenia, anemia, thrombocytopenia, and renal dysfunction. Foscarnet has been associated with cytopenia, renal insufficiency, electrolyte abnormalities, and seizures. For patients taking these medications, perform complete blood count with differential and check electrolytes and creatinine twice weekly during initial therapy and once weekly during maintenance therapy. Cidofovir has been associated with renal insufficiency and ocular hypotony. For patients taking cidofovir, check creatinine and blood urea nitrogen and perform urinalysis (for proteinuria) before each dose. Intraocular pressure must be checked at least every 6 months.

Patient Education

- Educate patients about the importance of ART in treating CMV. Urge patients to start ART if they have not done so already.
- Patients with CMV retinitis may have to remain on suppressive therapy for life to prevent blindness. Patients with CMV esophagitis or enteritis usually see improvements within 2-4 weeks after starting therapy.
- Treatment of CMV retinitis halts progression of the infection but does not reverse the damage already done to the retina. Warn patients that vision will not return to pre-CMV status.
- Advise patients to report any visual deterioration immediately. Retinal detachment or progression of CMV must be treated immediately to avoid further vision loss.
- For patients who experience significant vision loss, offer referral to education, training, and support services to help them adjust.
- With gastrointestinal disease, recurrence of symptoms warrants repeat endoscopy. Advise patients to report any recurrence of symptoms.
- Adverse reactions to current therapies are common. Educate patients about these and advise them to promptly report any adverse reactions.
- Help patients cope with the possibility of therapeutic failure, and, in the case of CMV retinitis, permanent loss of vision.
- Teach patients how to maintain indwelling venous access lines, if used. Have patients demonstrate these techniques before discharge.

Gonorrhea and Chlamydia

Background

Gonorrhea, caused by *Neisseria gonorrhoeae* (GC), and chlamydia, caused by *Chlamydia trachomatis* (CT), are sexually transmitted diseases (STDs). These infections may be transmitted during oral, vaginal, or anal sex; they also can be transmitted from a mother to her baby during delivery and cause significant illness in the infant.

Both organisms can infect the urethra, oropharynx, and rectum in women and men; the epididymis in men; and the cervix, uterus, and fallopian tubes in women. Untreated GC or CT infection in women may lead to pelvic inflammatory disease (PID), which can cause chronic pelvic pain and scarring of the fallopian tubes that results in infertility or ectopic pregnancy (tubal pregnancy). *N. gonorrhoeae* can cause disseminated infection involving the skin, joints, and other systems. Infection with GC or CT may facilitate transmission of HIV to HIV-uninfected sex partners.

Certain strains of CT can cause lymphogranuloma venereum (LGV). This infection is common in parts of Africa, India, Southeast Asia, and the Caribbean. Although relatively uncommon in the United States, outbreaks among men who have sex with men (MSM) have been reported in recent years. LGV may cause genital ulcers, followed by inguinal adenopathy; it also can cause proctocolitis with anorectal discharge, tenesmus, and pain.

Patients with symptoms of gonorrhea or chlamydia should be evaluated and treated as indicated below. Although GC or CT urethral infections in men may cause symptoms, infection in women and oral or rectal infections in men often cause no symptoms. Thus, sexually active individuals at risk of GC and CT exposure should receive regular screening for these infections as well as for syphilis and other STDs; for most patients, this should be at least annually, and every 3-6 months for persons at higher risk (see chapter *Initial and Interim Laboratory and Other Tests*).

S: Subjective

Symptoms will depend on the site of infection (e.g., oropharynx, urethra, cervix, rectum). Symptoms are not present in many patients, thus it is important to screen all patients at risk of STDs.

If symptoms are present, **women** may notice the following (depending on site of infection):

- Vaginal discharge
- Pain with sexual intercourse
- Pain or burning on urination
- Abdominal or pelvic pain
- Sore throat
- Rectal discharge
- Anal discomfort or tenesmus

If symptoms are present, **men** may notice the following (depending on site of infection):

- Pain or burning on urination
- Urethral discharge
- Testicular tenderness or pain
- Sore throat
- Rectal discharge
- Anal discomfort or tenesmus

During the history, ask the patient about the following:

- Any of the symptoms listed above, and their duration
- Previous diagnosis of GC, CT, or other STD
- New sex partner(s); number and gender of partners

- Unprotected sex (oral, vaginal, anal; receptive or insertive)
- For women: last menstrual period, and whether the patient could be pregnant; use of an intrauterine device

O: Objective

Physical Examination

During the physical examination, check for fever and document other vital signs.

For **women**, focus the physical examination on the mouth, abdomen, and pelvis. Inspect the oropharynx for discharge and lesions; check the abdomen for bowel sounds, distention, rebound, guarding, masses, and suprapubic or costovertebral angle tenderness; perform a complete genital and vaginal examination for abnormal discharge or bleeding; check for uterine, adnexal, or cervical motion tenderness; and search for pelvic masses or adnexal enlargement. Check the anus for discharge and lesions; perform anoscopy if symptoms of proctitis are present. Check for inguinal lymphadenopathy. Check the skin for rashes and lesions.

For **men**, focus the physical examination on the mouth, genitals, and anus/rectum. Check the oropharynx for lesions, the urethra for discharge, the external genitalia for tenderness, masses, or lesions, and the anus for discharge and lesions; perform anoscopy if symptoms of proctitis are present. Check for inguinal lymphadenopathy. Check the skin for rashes and lesions.

A: Assessment

A partial differential diagnosis includes the following:

- Urinary tract infection
- Dysmenorrhea
- Appendicitis
- Cystitis

- Proctitis
- PID
- Irritable bowel syndrome
- Pyelonephritis

P: Plan

Diagnostic Evaluation

Test for oral, urethral, or anorectal infection, according to symptoms and anatomic site(s) of possible exposures. Perform testing for both gonorrhea and chlamydia (testing for pharyngeal CT infection generally is not recommended although the CT pharyngeal test often accompanies the GC pharyngeal nucleic acid amplification test [NAAT]). The availability of the various testing methods varies according to the specific clinic site. Consider the following:

- NAAT: urine specimens (first stream) and urethral (men), vaginal, and endocervical swab specimens; also used with pharyngeal and rectal swab specimens (laboratory must meet Clinical Laboratory Improvement Amendments [CLIA] specifications and establish validity in nongenital specimens); recommended unless GC antibiotic resistance is suspected
- GC culture (oropharynx, endocervix, urethra, rectum) – consider especially if antibiotic resistance is suspected
- Gram stain of urethral discharge for evidence of GC
- Serologic tests (complement fixation test) if LGV is suspected

Treatment

Treatments for gonorrhea and chlamydia are indicated below. Fluoroquinolone-resistant GC is widespread in the United States and throughout the world. Thus, the U.S. Centers for Disease Control and Prevention (CDC) recommends that fluoroquinolones not be used for treatment of GC. Similarly, resistance

of GC to cephalosporins is emerging, though third-generation cephalosporins are effective against most GC strains in the United States and remain the only recommended treatment for GC. GC strains with decreased susceptibility to azithromycin also have been reported, and azithromycin should be used to treat GC only for select patients in whom treatment with a cephalosporin should be avoided.

Adherence is essential for treatment success. Single-dose treatments maximize the likelihood of adherence and are preferred. Other considerations in choosing the treatment include antibiotic resistance, cost, allergies, and pregnancy. For further information, see the CDC STD treatment guidelines (see “References,” below); treatments should be given in accordance with these guidelines.

Any sex partners within the past 60 days, or the most recent sex partner from >60 days before diagnosis, also should receive treatment. Patients should abstain from sexual activity for 7 days after a single-dose treatment or until a 7-day treatment course is completed. Reinfection with GC or CT is likely if reexposure occurs; patients with either GC or CT should be rescreened 3 months after treatment.

Treatment of Gonorrhea

Treatment options include the following (see the full CDC STD treatment guidelines, referenced below); the current guidelines emphasize that dual therapy for GC should be given, with ceftriaxone plus either azithromycin or doxycycline. Ceftriaxone is the recommended cephalosporin for GC infection at any anatomic site. Coadministration of azithromycin or doxycycline is intended to improve the likelihood of cure and may decrease the risk of emergent cephalosporin resistance; it should be given, even if test results for CT are negative.

Recommended regimen (for GC of all anatomic sites)

- Ceftriaxone 250 mg IM injection in a single dose, **plus** azithromycin 1 g PO in a single dose or doxycycline 100 mg PO BID for 7 days

Alternative regimens (for GC of pharynx, cervix, urethra, and rectum)*

- If ceftriaxone is not available: cefixime 400 mg PO in a single dose (tablet or oral suspension), plus azithromycin or doxycycline, as above
 - If severe cephalosporin allergy: azithromycin 2 g PO in a single dose
- * If an alternative regimen is used, a test of cure (TOC) should be done in 1 week: GC culture (preferred) or NAAT. A positive NAAT result should be followed by confirmatory culture and antimicrobial susceptibility testing. Possible cephalosporin treatment failures should be reported immediately to the local or state health department.

If penicillin or cephalosporin allergy:

- Cephalosporins are contraindicated for use only in patients with a history of severe reaction to penicillin.
- Consultation with an infectious disease specialist is recommended.
- Consider azithromycin 2 g PO, with TOC, as above.
- Consider cephalosporin treatment following desensitization.

Note: Fluoroquinolones are not recommended for treatment of gonococcal infection because of widespread resistance in the United States.

Please see full CDC STD treatment guidelines regarding treatment of PID, epididymitis, and disseminated gonococcal infection.

Treatment of Chlamydia

(See the full CDC STD treatment guidelines, referenced below.)

Recommended regimens

- Azithromycin 1 g PO in a single dose
- Doxycycline 100 mg PO BID for 7 days

Alternative regimens

- Erythromycin base 500 mg PO QID for 7 days
- Erythromycin ethylsuccinate 800 mg PO QID for 7 days
- Levofloxacin 500 mg PO QD for 7 days (see Note above)
- Ofloxacin 300 mg PO BID for 7 days (see Note above)

Treatment of LGV

Recommended regimens

- Doxycycline 100 mg PO BID for 21 days

Alternative regimens

- Erythromycin base 500 mg PO QID for 21 days
- Azithromycin 1 g PO once weekly for 3 weeks (limited data)

For recent sex partners (within 60 days before the onset of patient's symptoms), test for urethral or cervical CT, treat with azithromycin 1 g PO in a single dose or doxycycline 100 mg PO BID for 7 days.

Treatment During Pregnancy

Use of fluoroquinolones and tetracyclines should be avoided during pregnancy.

Recommended GC regimens

- Ceftriaxone 250 mg IM + azithromycin 1 g PO in a single dose

Recommended CT regimens

- Azithromycin 1 g PO in a single dose
- Amoxicillin 500 mg PO TID for 7 days

Alternative CT regimens

- Erythromycin base 500 mg PO QID for 7 days
- Erythromycin base 250 mg PO QID for 14 days
- Erythromycin ethylsuccinate 800 mg PO QID for 7 days
- Erythromycin ethylsuccinate 400 mg PO QID for 14 days

Follow-Up

- For both GC and CT, evaluate the patient's sex partners; treat them empirically if they had sexual contact with the patient during the 60 days preceding the patient's onset of symptoms. Some clinics provide empiric treatment for partners via "partner packs," or a treatment regimen that the patient takes to the partner(s); this approach may be effective, particularly for CT, if the partner(s) is/are unlikely to come to the clinic for evaluation and treatment.
- Most recurrent infections come from sex partners who were not treated.
- The CDC recommends rescreening all patients 3 months after GC or CT treatment (for possible reinfection).
- For pregnant women with CT, retest (by NAAT) 3 weeks after completion of treatment.

- If symptoms persist, evaluate for the possibility of reinfection, treatment failure, or a different cause of symptoms. If treatment failure is suspected, perform culture and antimicrobial sensitivity testing.
- Screen for GC, CT, syphilis, and other STDs at regular intervals according to the patient's risk factors. The sites of sampling (e.g., pharynx, urethra, endocervix, anus/rectum) will be determined according to the patient's sexual exposures.
- Evaluate each patient's sexual practices with regard to the risk of acquiring STDs and of transmitting HIV; work with the patient to reduce sexual risks.

Patient Education

- Instruct patients to take all of their medications. Advise patients to take medications with food if they are nauseated and to call or return to clinic right away if they experience vomiting or are unable to take their medications.
- Sex partners from the previous 60 days need to be tested for sexually transmitted pathogens, and treated as soon as possible with a regimen effective against GC and CT, even if they have no symptoms. Advise patients to inform their partner(s) that they need to be tested and treated. Otherwise, patients may be reinfected.
- Advise patients to avoid sexual contact until the infection has been cured (in themselves and in their partners) at least 7 days.
- Provide education about sexual risk reduction. Instruct patients to use condoms with every sexual contact to prevent reinfection with GC or CT, to prevent other STDs, and to prevent transmission of HIV to sex partners.

Hepatitis B Infection

Background

Hepatitis B virus (HBV) is the most common cause of chronic liver disease worldwide. Chronic HBV can cause necroinflammation and over time can cause hepatic fibrosis and eventually cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC). It is estimated that 350 million people have chronic HBV infection, with approximately 1.25 million of them in the United States. HBV is a DNA virus that is spread through exposure to infected blood and body fluids. It typically is transmitted by parenteral, sexual, and vertical exposures, but may be transmitted through person-to-person contacts among household members, especially because HBV can survive outside the body for long periods of time. Because HIV and HBV share transmission routes, up to 90% of HIV-infected patients have evidence of HBV exposure. In the United States, chronic HBV infection has been identified in 6-15% of HIV-infected persons.

The epidemiology of HBV infection varies by geographic region. In Southeast Asia and sub-Saharan Africa, HBV is highly prevalent and almost all infections occur perinatally or during early childhood. In the United States and Western Europe, most infections occur through sexual exposure or high-risk injection drug-use behavior.

To identify patients with HBV coinfection, and to identify and vaccinate susceptible individuals, all HIV-infected persons should be tested for HBV (see chapters *Initial and Interim Laboratory and Other Tests* and *Immunizations for HIV-Infected Adults and Adolescents*). In addition, all patients with chronic HBV infection should be tested for HIV and all patients with evidence of prior resolved HBV infection should be strongly considered for HIV testing.

It is universally recommended that HBV vaccination should be given to all HIV-infected persons who are susceptible to HBV infection (see “Interpreting HBV test results,” below, and chapter *Immunizations for HIV-Infected Adults and Adolescents*). It is recommended that the vaccine series be given when CD4 counts are >200 cells/ μL , if possible, as doing so is associated with higher rates of vaccine response, but vaccination should not be delayed for persons with lower CD4 counts.

The natural history of HBV infection is complex and dynamic, with phases of active replication and of inactive replication, and fluctuating alanine aminotransferase (ALT) levels. The likelihood of developing chronic HBV after exposure varies with age, mode of infection, and immunocompromised status. Among newborns born to HBV-infected mothers, 90% develop chronic hepatitis B, whereas 30% of exposed infants and young children and $<5\%$ of exposed adults develop chronic infection. Most adults who become infected with HBV are able to clear the virus without treatment, and they subsequently become immune to HBV. Chronic progressive HBV can lead to cirrhosis and then to decompensated liver disease including ascites, portal hypertension, esophageal varices, coagulopathy, thrombocytopenia, and hepatic encephalopathy. HCC can develop in patients with or without cirrhosis; in fact, 30-50% of HCC cases attributable to HBV occur in the absence of cirrhosis.

HRSA HAB Performance Measures

Percentage of patients with a diagnosis of HIV who completed the vaccination series for hepatitis B

(Adult and Adolescent measure)

Factors associated with increased rates of cirrhosis include the following:

- Longer duration of infection
- HBV genotype C
- High levels of HBV DNA
- Alcohol consumption
- Smoking
- Aflatoxin exposure
- Coinfection with HIV
- Coinfection with hepatitis D virus
- Coinfection with HCV

Factors associated with increased rates of HCC include the following:

- Male gender
- Family history of HCC
- Older age
- Presence of HBV envelope antigen (HBeAg); history of reversion from anti-HBe to HBeAg
- High levels of HBV DNA
- Presence of cirrhosis
- HBV genotype C
- Core promoter mutation
- Coinfection with HCV

Among individuals who are not taking ART, HIV infection significantly modifies the natural history of HBV infection. HIV infection appears to increase the risk of developing chronic HBV infection after acute HBV, and it is associated with a higher level of HBV DNA replication and lower rates of spontaneous HBeAg seroconversion. In patients with chronic HBV, HIV coinfection is associated with faster progression of liver disease and cirrhosis and increased rates of liver-related deaths. Although HIV coinfection itself is not known to increase the risk of HCC development, it does increase the risk of cirrhosis, which in turn increases the risk of HCC.

Treatment of HIV infection with effective ART has increased the life expectancy of HIV-infected patients in recent years, and paradoxically has given HIV/HBV-coinfected patients a longer lifespan during which cirrhosis may develop. Partly for this reason, the relative proportion of deaths attributable to liver disease among HIV-infected patients is rising. On the other hand, ART can positively impact the natural history of HBV infection. Effective ART can improve patients' immune responses against HBV. ART also may be used to cotreat HBV in coinfecting patients. Several of the nucleoside analogues (NRTIs) used against HIV also are active against HBV, and these should be included in an ART regimen to treat both HIV and HBV for coinfecting persons (see "Antiviral Treatment of Chronic HBV Infection," below). Withdrawal of NRTIs with anti-HBV activity can precipitate a reactivation of HBV. ART that contains anti-HBV NRTIs also may prevent acute infections in patients who are receiving them. Current U.S. Department of Health and Human Services (HHS) guidelines recommend initiation of ART (and cotreatment of HBV) for all persons with HIV/HBV coinfection.

S: Subjective

Persons with acute HBV infection may have symptoms including fatigue, nausea, vomiting, arthralgias, fever, right upper quadrant pain, jaundice, dark urine, and clay-colored stools. Some patients may have no symptoms at all.

Persons with chronic HBV, even with early cirrhosis, may be asymptomatic or may experience only fatigue or mild right upper quadrant tenderness. Patients with decompensated cirrhosis may experience increased abdominal girth, easy bruising, telangiectasis, pruritus, gastrointestinal bleeding, or altered mentation. Patients with early or small HCC may have no additional symptoms or may develop significant abdominal pain, weight loss, nausea, or bone pain.

Ask patients with known HBV infection about symptoms that suggest complications of HBV such as cirrhosis, decompensation, risk factors for worsening liver disease, and hepatotoxins. Questions should address the symptoms listed above, and the following:

- Fatigue
- Weight loss
- Impaired concentration
- Chronic HCV
- Alcohol intake
- Substance use
- Antiretroviral (ARV) medications that may cause hepatotoxicity (e.g., didanosine, protease inhibitors, nevirapine, maraviroc)
- Medications with potential for hepatotoxicity or accumulation in persons with liver disease (e.g., acetaminophen, benzodiazepines, opiates)

O: Objective

Measure vital signs.

Perform a physical examination to include evaluation of the following:

- Head, ears, eyes, nose, throat (HEENT): temporal wasting, icterus, gum bleeding
- Heart and lungs: signs of congestive heart failure
- Chest: gynecomastia
- Abdomen: caput medusa, venous prominence, distention, signs of ascites, hepatomegaly, splenomegaly
- Extremities: edema
- Neurologic: alertness, mental status, asterixis
- Skin: jaundice, palmar erythema, petechiae, ecchymoses, spider angiomas

P: Plan

HBV Testing

As discussed above, all HIV-infected persons should be screened for HBV surface antigen (HBsAg), HBs antibody (HBsAb), and HBV core antibody (total) (HBcAb-total) and be vaccinated if not immune (see chapter *Immunizations for HIV-Infected Adults and Adolescents*).

Nonimmune persons with elevated transaminases or signs or symptoms of acute or chronic liver disease should be retested for HBV and HCV infection.

Interpreting HBV test results

Routine baseline HBV serologic screening tests for HIV-infected individuals are outlined in Table 1.

Markers of chronic hepatitis B can manifest in a number of patterns (see Table 1).

Table 1. Interpreting HBV Laboratory Tests

	Acute Hepatitis B	Recovery from Acute Hepatitis B	Chronic HBeAg+ Disease	Chronic HBeAg- Disease	Occult Hepatitis B	Successful Vaccination	Isolated HBcAb
HBsAg	X (may clear)		X	X			
Anti-HBs		X				X	
Anti-HBc IgM	X (may be the only marker during window period)						
Anti-HBc	X	X	X	X	X		X
HBeAg	X		X		X		
Anti-HBe		X (in some cases)		X			X (in some cases)
DNA* (PCR if required)	X		X	X	X		(in rare cases, may be +)

* Absence of detectable HBV DNA does not rule out chronic HBV infection in patients who are on ARVs with anti-HBV activity.

Because of the complexity of HBV diagnosis and test interpretation, it is important to test for HBsAg, HBcAb, and HBsAb. If the result for either HBsAg or HBcAb is positive, then test for HBV DNA. The presence of HBsAg for >6 months indicates chronic HBV infection, but detectable HBV DNA is required for the diagnosis. HBV DNA should be tested before initiation of ART, if possible, as NRTIs with anti-HBV activity may suppress HBV viremia and interfere with diagnosis. Some persons with HIV infection can have chronic HBV infection with high HBV DNA levels and hepatic inflammation while testing negative for HBsAg and positive only for HBcAb. This sometimes is termed “occult hepatitis B infection.” Patients with chronic HBV may test either positive or negative for HBeAg. Patients with inactive chronic HBV are positive for HBsAg but have persistently normal ALT levels, low-level or no detectable HBV DNA, and negative HBeAg results. Ongoing viral replication and infectiousness is indicated by the presence of HBV DNA or a positive result for HBeAg.

Markers of immunity or previous exposure to HBV also can manifest in a number of patterns (see Table 1). Successful vaccination to HBV (in someone who has never been infected) will result in positive HBsAb but negative HBcAb results. Prior exposure to HBV may result in positive HBcAb and HBsAb findings, indicating the development of immunity. However, prior exposure may present as positive HBcAb only, with negative results for HBsAb, HBsAg, and HBV DNA. This pattern shows that the patient was previously infected with hepatitis B but did not develop chronic infection, and lost the HBsAb. This sometimes is termed “isolated core Ab,” and it is seen more commonly in patients coinfectd with HIV or HCV. It is not known whether patients who display this pattern would have sufficient immunity to ward off another HBV infection if they were reexposed; current guidelines recommend the standard HBV vaccination series, followed by a check of HBsAb.

In acute HBV infection, HBV DNA will be detectable before HBsAg, if highly sensitive nucleic acid testing is used. Otherwise, HBsAg is the only marker detected during the first 3-5 weeks after infection. HBcAb develops at approximately 6 weeks after infection and both immunoglobulin M (IgM) and immunoglobulin G (IgG) will be evident. The IgM will decline within 6 months but the IgG will persist for life. Among individuals who recover from acute HBV infection, HBeAg typically seroconverts to HBeAb at approximately 3 months whereas, for those who develop chronic HBV infection, HBeAg typically persists for years.

Diagnostic Evaluation of Acute HBV Infection

When approaching the diagnosis of a patient with acute hepatitis B infection, the following steps should be taken:

1. Obtain history and perform physical examination.

Determine the time and route of infection if possible. Take a complete history, including HIV disease course and treatment, and other medical history. Perform physical examination, focusing on evidence of acute liver dysfunction.

2. Assess HBV replication serially.

As soon as acute infection is suspected, check HBsAg, HBV DNA, HBeAg, HBeAb, ALT, HBcAb-IgM, and HBsAb. HBsAg usually can be detected by 4 weeks (the range of detectability is 1-9 weeks). HBcAb-IgM is detectable at the onset of symptoms.

When ALT is abnormal and rising, additional tests of liver function should be serially evaluated until it is clear that ALT is trending back down. Tests should include albumin, total bilirubin, prothrombin time, and platelet count.

3. Determine whether HBV infection resolves or persists as chronic HBV infection.

If the HBsAg is still present at 6 months after acute infection, the HBV infection has persisted and the patient has chronic hepatitis B infection.

Initial Diagnostic Evaluation of Chronic HBV Infection

When approaching the diagnosis of a patient with chronic HBV infection, the following steps should be taken:

- Take a complete history, including family history of HBV or HCC, and HIV disease course and treatment. Perform physical examination.
- Assess HBV replication to determine HBV DNA level, HBeAg and HBeAb serostatus, and ALT level. Note that HBV DNA levels may be difficult to interpret in patients who are on ARVs that have anti-HBV activity (HBV level may be low or undetectable because of these medications).
- Assess liver disease – check complete blood cell count with platelet count, albumin, total bilirubin, transaminases (especially ALT), and prothrombin time.
- Assess for possible overlying liver diseases (e.g., HCV, alcoholic liver disease, fatty liver disease).
- Consider liver biopsy to assess histological degree of inflammation and fibrosis, especially if the result would affect the decision to use treatment.
- Screen for HCC at baseline via ultrasound.
- Test for hepatitis A antibodies (IgG) and vaccinate against hepatitis A if not immune.

Long-Term Monitoring of Chronic HBV Infection

It should be noted that current HHS guidelines strongly recommend treatment of both HIV and HBV in all coinfecting persons. Nonetheless, some patients may wish to defer treatment or may not tolerate treatment. For those patients who are not on treatment for HBV, regular monitoring of HBV replication and liver function should be performed.

For patients with the following seromarkers, recommendations are as indicated:

Negative HBeAg, low ALT, and low-level DNA (<2,000 IU/mL) (inactive HBV):

HBV DNA, HBeAg, and ALT testing should be performed every 3 months for the first year to determine whether the virus is truly inactive. If it remains inactive (with negative HBeAg, normal ALT, and low-level DNA), monitoring can continue every 6-12 months; some specialists recommend more frequent monitoring.

Negative HBeAg, elevated ALT, and high HBV DNA (>20,000 IU/mL):

Biopsy should be considered, and treatment should be considered. If treatment is not started, monitoring should occur every 3 months.

Negative HBeAg, moderately elevated ALT, and moderately elevated DNA (2,000-20,000 IU/mL):

Follow-up should be performed every 3-6 months if treatment is not started.

Positive HBeAg, moderately elevated ALT:

Monitoring should be performed every 3 months and, if ALT is persistently elevated, a biopsy should be considered to guide the decision regarding initiation of HBV treatment.

Positive HBeAg, high HBV DNA (>20,000 IU/mL) but low-level ALT:

Monitoring should be performed every 3-6 months to check for changes in ALT. If ALT rises significantly, treatment should be considered.

Cirrhosis:

Treatment should be considered. For patients who are not treated, monitoring should be performed every 3-6 months.

Antiviral Treatment of Chronic HBV Infection

HHS ARV guidelines and Centers for Disease Control and Prevention opportunistic infection guidelines recommend treatment of both HIV and HBV in all coinfecting persons. The goals and markers of HBV treatment for HIV/HBV-coinfecting patients are the same as for HBV-monoinfected patients.

The goals of treatment are as follows:

- To decrease progression of liver disease
- To prevent development of cirrhosis
- To prevent development of HCC

Treatment endpoints for the HBV/HIV-coinfecting population are not well defined but efficacy is determined by the following measures:

- HBeAg seroconversion to HBeAb (this is harder to achieve for coinfecting patients than for HBV-monoinfected persons)
- HBV DNA suppression
- ALT normalization, which usually follows the changes in HBV DNA

The timing of treatment and choice of treatment for HBV/HIV-coinfecting patients are important.

Treatment for HIV and HBV:

- All HIV/HBV coinfecting patients should be treated for both HIV and HBV infections, if possible.
 - If treatment for HIV is to be started, HBV should be treated concurrently with the HIV by using a potent ART regimen that includes two NRTIs that are active against both viruses (tenofovir + emtricitabine or tenofovir + lamivudine), if possible. If tenofovir is contraindicated, entecavir or another anti-HBV drug should be used (with emtricitabine or lamivudine) to construct a two-drug therapy for HBV, and the HIV ART regimen should be designed for complete HIV suppression (see Table 2). In this situation, liver biopsy to stage disease is not necessary because HBV treatment will be undertaken (incorporated into the HIV regimen). Note that treatment of HBV with a single NRTI is not recommended, because of the risk of HBV resistance; if tenofovir cannot be used, entecavir (plus combination ART) is the preferred alternative (see Table 2).
 - Most patients receiving ART who are treated for HBV will require HBV treatment indefinitely (lifelong).
- HBeAg negative, ALT is more than two times the ULN and HBV DNA >2,000 IU/mL: consider HBV treatment.
 - HBeAg positive, HBV DNA >20,000 IU/mL, but ALT is less than two times the ULN: can use a biopsy to determine the need for HBV treatment.
 - HBeAg negative, DNA >2,000 IU/mL, but ALT is less than two times the ULN: can use a biopsy to determine the need for HBV treatment.
 - Any patient with cirrhosis (if not decompensated) and a detectable DNA level: should be considered for HBV treatment, regardless of HBeAg status and regardless of ALT level.
 - Patients with decompensated cirrhosis should not be treated for HBV but should be referred for transplant.
 - Some specialists recommend HBV treatment for all patients with detectable HBV DNA, particularly if ALT is elevated or inflammation or fibrosis is seen on liver biopsy.
 - If a decision is made to treat HBV but not HIV, HBV treatment should not include agents that are dually active, as that could lead to early HIV resistance. This limits choices to pegylated interferon alfa-2a (although it has not been studied in HIV/HBV-coinfecting patients) or adefovir dipivoxil. Tenofovir, lamivudine, emtricitabine, entecavir, and telbivudine should not be used as monotherapy for HIV/HBV-coinfecting patients, because HIV (and HBV) resistance may develop (see Table 2).

Treatment for HBV alone:

- If HBV treatment is indicated, HIV infection should be treated concurrently, if possible, as stated above. If treatment for HIV is deferred, the hepatitis B should be treated if the patient otherwise meets criteria for HBV treatment (see below).
 - Inactive chronic hepatitis B (HBV DNA is <2,000 IU/mL, HBeAg is negative, and ALT is not elevated): the HBV can be monitored and does not require treatment.
 - HBeAg positive, ALT is more than two times the upper limit of normal (ULN), and HBV DNA >20,000 IU/mL: consider HBV treatment.

Table 2. Antiviral Therapies for Chronic HBV Infection

	Lamivudine	Emtricitabine	Tenofovir	Adefovir	Entecavir	Telbivudine	Pegylated Interferon
Dual activity against HBV and HIV	Yes	Yes	Yes	No (at the low HBV treatment dosage), but theoretical concern remains	Yes	Possibly	No
Recommended for use in HIV/HBV coinfection	With tenofovir, as part of fully suppressive ART	With tenofovir, as part of fully suppressive ART	With lamivudine or emtricitabine, as part of fully suppressive ART	If HIV is not being treated, or in combination with a lamivudine- or emtricitabine-containing ART regimen, if tenofovir is not used	With fully suppressive ART	With fully suppressive ART	If HIV is not being treated
Loss of HBV DNA	40-44%		76%	21%	67%	60%	25%
HBeAg seroconversion	16-21%		21%	12%	21%	22%	27-32%
Class	Nucleoside analogue	Nucleoside analogue	Nucleotide analogue	Nucleotide analogue	Nucleoside analogue	Nucleotide analogue	Interferon

Additional points about treatment for HIV/ HBV-coinfected patients:

- When lamivudine is used as a single agent, HBV resistance develops in many patients by 1-2 years. Although combination therapy has not been well studied, specialists recommend using dual-NRTI combinations that have activity against HBV (lamivudine + tenofovir, or emtricitabine + tenofovir [Truvada]) as part of the ARV regimen, to treat HBV and to prevent HBV resistance.
- Some patients treated with ART may experience worsening of HBV symptoms

and laboratory markers in the weeks after ART initiation, because of immune reconstitution inflammatory reactions. Hepatic decompensation owing to immune reconstitution must be distinguished from other causes, such as medication toxicity, or other infection. Liver function tests should be monitored closely for patients starting ART.

- Some ARV medications are hepatotoxic and should be avoided or used cautiously. These include nevirapine, tipranavir, and high-dose ritonavir. Numerous other medications (e.g., fluconazole, isoniazid) are hepatotoxic

and can pose problems for patients with impaired liver function.

- Discontinuation of HBV medications in patients with HIV/HBV coinfection may cause a flare of liver disease. Be very cautious when discontinuing HBV-active medications from an anti-HIV ART regimen. If the HBV DNA is suppressed, options include continuing the HBV-active ARVs, even if there is HIV resistance (modify the other parts of the ART regimen for maximal HIV suppression) or substituting other HBV-active medications to avoid rebound liver inflammation and decompensation. For example, if it is decided to discontinue a lamivudine/tenofovir-containing regimen in an HIV/HBV-coinfected patient on ART, consider starting interferon or possibly adefovir to maintain activity against HBV. If HBV therapy is discontinued and a flare occurs, consider reinstating HBV therapy as soon as possible.
- Limited data exist on treatment of HBV in the setting of HIV and HCV. Consider consultation with an expert if optimal timing for treatment of the three infections is not clear.

Screening for HCC in patients with chronic HBV infection:

Persons with chronic HBV are at increased risk of developing HCC. Note that HCC may occur even in the absence of cirrhosis. HCC screening should be performed every 6-12 months using ultrasound (computed tomography [CT] is an alternative); alpha-fetoprotein should be monitored if ultrasound reliability is low.

HBV-infected patients who should be screened for HCC include the following:

- Anyone with cirrhosis
- Anyone over age 40 with elevated ALT or HBV DNA level of >2,000 copies/mL
- Asian men aged >40
- Asian women aged >50
- Persons of African descent aged >20
- Anyone with a family history of HCC

Interventions to slow progression and prevent complications

Persons with HCV infection should be counseled to avoid exposure to hepatotoxins, including alcohol and hepatotoxic medications (e.g., acetaminophen in large doses, fluconazole, isoniazid). Heavy alcohol use is a risk factor for increasing rate of fibrosis. It is not clear what degree of alcohol consumption is safe, so many experts recommend complete abstinence from alcohol.

- No specific dietary measures are recommended.
- Patients who are not already immune to hepatitis A should be vaccinated against hepatitis A.
- Patients should be counseled on ways to avoid infection with hepatitis C.

Preventing transmission

All patients with HBV infection should receive individualized counseling on ways to reduce the risk of HBV transmission (including by sexual or needle-sharing behavior, perinatal routes, or household exposure), as appropriate.

Household members and sexual contacts should be vaccinated against HBV.

Women who are pregnant or considering pregnancy should consult with a specialist in both HBV and HIV to discuss ways of decreasing the infection risk for the fetus; this may include treatment for HBV and HIV. Infants born to coinfecting women should receive HBV immune globulin and start the HBV vaccine series within 12 hours after birth (with subsequent vaccine doses per usual protocol).

Patient Education

- Advise patients that most people with HBV will remain asymptomatic for several years. However, ongoing injury to the liver occurs during this time and can culminate in liver failure. Patients can slow the progression of damage by avoiding alcohol and any medications (including over-the-counter drugs and recreational drugs) that may damage the liver. Patients should contact their pharmacist or health care provider if they have questions about a specific medication or supplement.
- Advise patients that treatment for both HIV and HBV is recommended for anyone with HIV/HBV coinfection. ART can be used to treat both infections.
- As with HIV, patients must avoid passing HBV to others. Instruct patients not to share toothbrushes, dental appliances, razors, sex toys, tattoo equipment, injection equipment, or personal care items that may have blood on them. Emphasize to patients the importance of safer sex to protect themselves and their partners.
- Tell patients to discuss HBV with their sex partners, and suggest that partners be tested for HBV.
- Nonimmune sex partners and individuals in close contact with persons with chronic hepatitis B (e.g., family and household members) should be vaccinated.
- Pregnant women have a high risk of transmitting HIV or HBV to the fetus because each virus makes it easier to transmit the other. Women who are pregnant or considering pregnancy should talk with a specialist in HIV and HBV to discuss ways of decreasing the infection risk for the fetus.
- Advise patients who are on treatment for HBV that abrupt discontinuation of HBV treatment can cause a flare of HBV; they should not stop treatment without medical supervision.
- Certain ARV drugs are more likely than others to cause hepatotoxicity. Advise patients that their liver function should be monitored carefully if they start an ARV regimen, in order to determine whether the body is able to process the medicines.

Hepatitis C Infection

Background

In the United States, an estimated 2.7-3.9 million people are living with chronic hepatitis C virus (HCV) infection. Without treatment, 15% to 40% of persons living with the virus will develop cirrhosis or cancer, and HCV is the leading cause of liver transplantation in the United States. Hepatitis C-related mortality has been steadily increasing in recent years, and as the baby boomer generation ages, the rates of cirrhosis and hepatocellular carcinoma (HCC) are expected to rise.

As antiretroviral therapy (ART) has reduced AIDS-related mortality among HIV-infected patients, liver disease owing to HCV infection has become a leading cause of death and the sequelae of chronic HCV have increased. HCV is common among persons with HIV infection in the United States. It is estimated that 20-30% of the HIV-infected population in the United States is coinfecting with HCV, but the prevalence varies with risk factor for transmission. Among HIV-infected injection drug users and hemophiliacs, 70-95% may be coinfecting with HCV; among HIV-infected men who have sex with men (MSM), 1-12% are coinfecting with HCV. The U.S. Centers for Disease Control and Prevention and the U.S. Public Health Service recommend that all HIV-infected persons receive screening for HCV.

HCV is a single-stranded RNA virus that is transmitted mainly through blood exposure and, less commonly, through perinatal or sexual exposure. HCV is more likely than HIV to be transmitted via a bloodborne route; there is an approximately 10-fold greater risk of HCV transmission after needlestick exposure compared with the risk of HIV transmission, and the concentrations of HCV in a given volume of blood are greater than those of HIV. Perinatal transmission of HIV is more likely among women who are coinfecting with HIV and HCV than among women with HIV infection alone; similarly, perinatal transmission of HCV is more likely in coinfecting women than in those with HCV monoinfection. Breast-feeding is not known to transmit HCV, although HIV-infected women are advised against breast-feeding because of the risk of transmitting HIV.

Although sexual transmission of HCV is not efficient, 10% of acutely HCV-infected persons report no risk factor other than sexual contact with an HCV-infected partner. Many centers have reported an increase in acute HCV in MSM, and rates of sexual transmission of HCV appear to be higher in MSM than in the general population, especially among persons who are coinfecting with HIV. In HIV-infected MSM, outbreaks of acute HCV have been reported, with sexual activity as the risk factor for transmission. Risk factors associated with sexual transmission of HCV include the presence of coexisting sexually transmitted diseases, unprotected anal receptive sex, and use of recreational drugs.

The natural history of HCV infection is variable. Approximately 20% of monoinfected patients ultimately develop cirrhosis, whereas approximately 80% of patients develop some degree of fibrosis (without progression to cirrhosis); patients without cirrhosis typically remain asymptomatic. HCV can affect organ systems outside the liver, such as dermatological and renal systems, but its effects most commonly are limited to the liver. Coinfection with HIV adversely impacts the natural history of HCV infection. HIV/HCV-coinfecting patients have lower rates of spontaneous HCV clearance, higher HCV viral loads, lower rates of successful HCV treatment with interferon and ribavirin, faster progression to cirrhosis, and greater risk of developing liver decompensation, end-stage liver disease, and hepatocellular carcinoma (HCC). On the other hand, HCV coinfection does not appear to increase HIV- and AIDS-related complications or the success of HIV antiretroviral (ARV) treatment.

Acute HCV Infection

Persons with acute HCV infection typically are asymptomatic or have only mild symptoms. Patients who do present with new onset of jaundice, weakness, anorexia, abdominal pain, or malaise without a known cause should be tested for acute HCV infection. Symptoms usually subside after several weeks. Patients who present after a potential exposure, such as a needlestick injury, should be tested for acute infection whether or not they are symptomatic. Overall, approximately 15-30% of patients acutely infected with HCV will clear the virus spontaneously, and 70-85% of patients will develop chronic infection. However, there are few prospective studies on the natural history of acute HCV infection with preexisting HIV infection. Because it is difficult to establish the precise timing of HCV infection, prospective natural history studies are difficult to perform.

Chronic HCV Infection

For the majority of HCV patients, other than laboratory abnormalities, there are no clinical manifestations of infection until the late stages of cirrhosis. Cirrhosis develops in approximately 20% of HCV-monoinfected patients, usually 20 years or more from the time of infection. A higher proportion of HIV/HCV-coinfected patients are thought to develop cirrhosis, and at a faster rate. Once patients have developed cirrhosis, approximately 50% will decompensate within the first 5 years. Typically, the first sign of decompensation is the development of ascites. Of patients with cirrhosis, approximately 1-4% per year will develop HCC, or approximately 20% of cirrhotic patients in total. The median survival time from the onset of HCC is approximately 5 months, and the 1-year survival rate is 29%.

S: Subjective

Patients with HCV infection, whether acute or chronic, often have no symptoms, and the infection is discovered via screening tests or on workup of an abnormal liver test result. Patients with acute HCV infection typically are asymptomatic but may present with symptoms such as jaundice, abdominal pain, and malaise. If symptoms from acute infection develop, they usually do so within 4 weeks after infection has occurred. Most patients with chronic HCV cannot recall a time when they were acutely symptomatic, and HCV is detected because of an incidental finding of abnormal transaminases or through a screening test.

Ask patients with known chronic HCV infection about symptoms that suggest complications of HCV, such as cirrhosis, decompensated cirrhosis, or hepatocellular carcinoma. Additionally, ask patients about any risk factors for other liver injury, such as alcohol and hepatotoxic drugs, and about drugs whose metabolism may be affected by liver disease.

- Fatigue
- Weight loss
- Impaired concentration
- Chronic hepatitis B
- Alcohol intake
- Substance use
- ARVs that may cause hepatotoxicity (e.g., didanosine, protease inhibitors, nevirapine, maraviroc)
- Medications with potential for hepatotoxicity, or accumulation in persons with liver disease (e.g., acetaminophen, benzodiazepines, opiates)

O: Objective

Measure vital signs. Calculate body mass index (see chapter *Initial Physical Examination*).

Perform physical examination to include evaluation of the following:

- Head, eyes, ears, nose, and throat (HEENT): temporal wasting, icterus
- Heart and lungs: signs of congestive heart failure

- Chest: gynecomastia
- Abdomen: caput medusa, venous prominence, distention, signs of ascites, hepatomegaly, splenomegaly
- Extremities: edema
- Neurologic: alertness, mental status, asterixis
- Skin: jaundice, palmar erythema, petechiae, ecchymoses, spider angiomas

P: Plan

Diagnostic Evaluation

Acute HCV infection

After initial exposure, HCV RNA can be detected in blood within 1-3 weeks and is present at the onset of symptoms. Antibodies to HCV can be detected in only 50-70% of patients at the onset of symptoms, but in >90% after 3 months. Within an average of 4-12 weeks, liver cell injury is manifested by elevation of serum alanine aminotransferase (ALT). It is important to understand the timeline of these diagnostic tests in order to appropriately diagnose acute infection and follow for potential resolution versus persistent infection.

In patients with suspected acute HCV infection, check HCV antibody (IgG), HCV RNA, and ALT immediately and then weekly until the ALT has begun to decline and HCV antibody has seroconverted to positive status; consider checking interleukin-28B (IL28B) (see below). The seroconversion of HCV antibody establishes the diagnosis of acute infection. At that point, check the HCV RNA every 2-4 weeks for the following 3 months. If HCV RNA is still present at 3 months, strongly consider prompt initiation of treatment for acute HCV. If treatment is not initiated and RNA is still present at 6 months after infection, the likelihood of spontaneous clearance is extremely low, and the patient is diagnosed with chronic infection.

Chronic HCV Infection

The following tests are part of the evaluation of HCV infection.

HCV antibodies

All HIV-infected patients should be tested for HCV infection with the HCV antibody test. Patients with risk factors for HCV infection who test negative should be retested at regular intervals. A positive HCV antibody test result does not establish the diagnosis of active HCV infection but is evidence of exposure; HCV RNA must be checked (see below). In HIV-infected patients, the HCV antibody test result can be falsely negative, although this is rare. Therefore, if HCV infection is suspected in spite of a negative HCV antibody finding (e.g., because of a history of high-risk behavior, unexplained elevated ALT, or evidence of cirrhosis), the HCV RNA should be tested even if the HCV antibody result is negative.

HCV RNA

All patients who test positive for HCV antibody should have HCV RNA testing performed. As noted above, if patients have negative results on HCV antibody tests but persistently abnormal transaminases or suspected acute or chronic infection, HCV RNA testing should be performed.

The definition of chronic HCV infection is the presence of HCV RNA 6 months after the estimated time of infection. If a patient is HCV antibody positive but HCV RNA negative, the patient has cleared the HCV and does not have chronic HCV infection. False-positive HCV antibody results are possible but rare; they are more likely to occur in the setting of autoimmune disease.

There are quantitative RNA tests and qualitative RNA tests. Although both types of RNA tests are highly sensitive and specific, the qualitative tests can detect lower levels of viremia than the quantitative tests. The choice of RNA test can be important. The quantitative RNA tests will be reported as a value, with a measured

number of international units per milliliter (IU/mL). Quantitative tests are useful for determining the prognosis of HCV treatment and then monitoring while on HCV treatment. Qualitative RNA tests will be reported as a present or absent value, but without a numerical value. They are useful for serial testing during suspected acute infection and for determining whether spontaneous viral clearance has occurred, a sustained virological response has occurred during treatment, or a relapse has occurred after treatment.

Genotyping

There are six main HCV genotypes, numbered 1-6. Genotype 1 infections account for approximately 75% of HCV infections in the United States. In the absence of treatment, HCV genotypes are not associated with prognosis or progression of liver disease. However, the HCV genotype is one of the strongest predictors of response to HCV treatment and is a major factor in determining the appropriate treatment regimen for a patient. HCV genotyping should be performed once for all patients with detectable HCV RNA; it does not need to be repeated.

Subtyping

HCV genotypes are further divided by subtypes. Subtypes are termed 1a, 1b, 2a, 2b, among others. Subtypes are newly being recognized as predictors of treatment response, particularly with genotypes 1a and 1b. Additionally, a polymorphism, Q80K, in genotype 1a patients may become clinically significant in determining treatment regimens using some of the new HCV drugs.

IL28B testing

IL28B is a host genetic polymorphism on chromosome 19. Three different IL28B polymorphisms exist: C/C, C/T, and T/T. Patients with C/C type have higher rates of spontaneous clearance after acute HCV

infection, and much higher response rates to interferon-based HCV treatment, whereas patients with the C/T or T/T genotype have lower rates of spontaneous clearance and much lower response rates to treatment with interferon. With non-interferon-based regimens, the role of IL28B has not yet been determined. In regimens containing either sofosbuvir (with or without pegylated interferon) or simeprevir (with interferon), better response rates were seen in patients with IL28B CC than in those with non-CC types, but the differences were much less dramatic than in older regimens.

Alanine aminotransferase

Monitoring of ALT can be useful to assess acute infection, chronic liver inflammation, and response to HCV treatment. However, ALT does not always correlate with the degree of fibrosis; in addition, ALT can be persistently normal in 25% of HCV patients, including patients with cirrhosis or advanced liver disease. Small fluctuations in ALT usually are not clinically significant in HCV, though trends can be significant during or following HCV treatment.

Additional tests

Check complete blood cell count with platelet count, albumin, total bilirubin, and prothrombin time.

Test all patients for hepatitis B (HBsAg, anti-HBsAb, and anti-HBcAb). For patients with a positive HBsAg or a positive anti-HBcAb result (absent anti-HBsAb), test for active HBV infection (HBV DNA and HBeAg) (see chapter *Hepatitis B Infection*). Patients with a negative HBsAg and negative anti-HBsAb result should be vaccinated against HBV.

Test for hepatitis A virus (HAV) antibodies (IgG or total). All patients with a negative HAV antibody result should be vaccinated against HAV.

Imaging

Ultrasonography can be performed to screen for indications of cirrhosis or focal hepatic masses. Repeated ultrasound every 6 months to screen for HCC is recommended for patients with known cirrhosis or advanced fibrosis (stage 3). For noncirrhotic patients, regular repeated ultrasound is not recommended. Computed tomography (CT), magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT) are more expensive and generally are reserved for further evaluation of liver masses detected by ultrasound.

Fibrosis staging

For any patient with HCV, it is useful to determine the degree of fibrosis (scarring) in the liver. Fibrosis stage is one of the most important pieces of information in determining a patient's need for HCV treatment. Fibrosis is scored from F0 to F4, with 0 indicating no fibrosis and F4 indicating cirrhosis.

Tools that may be used to determine the severity of chronic liver disease include biopsy, imaging, and serologic tests.

For HIV/HCV-coinfected patients, liver disease may progress quickly. A biopsy or other fibrosis test may be useful in determining the stage of disease and in planning whether or when to initiate HCV treatment. If the test reveals more advanced fibrosis or cirrhosis, treatment should be considered relatively urgently, using currently available therapeutics. Conversely, if the test reveals only mild-to-moderate fibrosis, it may be preferable to defer treatment and monitor the patient, particularly as more effective and more tolerable therapies are anticipated to become available within the next few years.

Liver biopsy

Liver biopsy is used to define the degree of inflammation (the grade) and degree of fibrosis (the stage) to determine the need for HCV treatment. Biopsy has been the gold

standard method, and is the main technique used in the United States. Liver biopsy carries some risk, primarily from bleeding (the risk of significant bleeding or fatality is approximately 1/10,000). Patients with severe thrombocytopenia or coagulopathy should not undergo liver biopsy.

As HCV therapies evolve and demonstrate higher response rates, a biopsy may prove less of a determinant of when to initiate treatment than in years past. At this time, with few directly acting agents (DAA) available, biopsy may still be useful for determining whether a patient can safely wait for more effective regimens.

Fibroscan

Several noninvasive tests to determine fibrosis have been developed. Fibroscan (elastography) is a radiology test used to assesses liver shear wave speed (expressed in meters per second) and equivalent stiffness (expressed in kilopascal) in a rapid, simple, noninvasive, and painless way. The FDA approved the Fibroscan in 2013. For diagnosing cirrhosis (stage F4), the sensitivity and specificity were 87% and 91%, respectively, whereas for diagnosing moderate stages of fibrosis (F2-F3), the sensitivity and specificity were 70% and 84%, respectively.

Serologic tests

Several different scoring systems have been developed to estimate the degree of liver fibrosis based on serum biomarkers and other patient factors. For example, the Fibrosure test uses the measurements of alpha-2-macroglobulin, alpha-2-globulin (haptoglobin), gammaglobulin, apolipoprotein A1, GGT, and total bilirubin, as well as the age and sex of the patient. The currently available serologic tests are not as accurate as liver biopsy in distinguishing different stages of fibrosis, and none of these have been FDA approved.

Treatment

Overview of the Treatment of HCV

The goal of HCV treatment is to clear the HCV RNA from the bloodstream – making the virus undetectable – in order to slow or halt inflammation, fibrosis, and progression of liver disease, and to reduce risk of cirrhosis and HCC. Treatment success is defined as a sustained virological response (SVR). SVR is achieved when the HCV RNA becomes undetectable during treatment and remains undetectable after the completion of treatment. Originally, SVR was defined as the absence of HCV RNA 24 weeks (“SVR24”) after the completion of treatment. SVR12 (12 weeks after the end of treatment) is 99% predictive of SVR24, so recent studies often report this as the outcome measure. SVR correlates with clinical outcomes such as decreased risk of decompensation, decreased risk of HCC, and decreased risk of liver-related death. Most experts consider SVR to represent “cure” of HCV. It is important, however, to remember that this is a cure of the chronic viral hepatitis infection, but it is not the same as “curing” the damage to the liver.

Pegylated interferon and ribavirin

The standard of care in the treatment of chronic HCV from 2001 to 2011 was the combination of pegylated interferon (PEG-IFN) alfa-2a and ribavirin, for both HCV-monoinfected and HIV/HCV-coinfected patients. Response rates varied by host and viral factors, among them HIV coinfection, HCV genotype, stage of liver disease, HCV viral load, race/ethnicity, and IL28B type. Overall, HCV-monoinfected genotype 1 patients have had SVR rates of 42-46% and monoinfected genotype 2/3 patients have had SVR rates of 70-80% with PEG-IFN + ribavirin. HIV/HCV-coinfected patients have had much lower response rates, in the range of 14-38%. Treatment was limited by these poor response rates as well as by multiple complete

and relative contraindications to interferon or ribavirin, multiple side effects of both drugs but especially interferon, and the cost and complexity of care for both patients and providers.

Telaprevir and Boceprevir

In 2011, the HCV protease inhibitors boceprevir and telaprevir were approved for genotype 1 HCV. These were the first direct acting antivirals (DAAs) available for treatment of HCV. With use of these agents in combination with PEG-IFN and ribavirin, treatment response rates in HCV-monoinfected genotype 1 patients were much higher than with PEG-IFN + ribavirin alone. In HIV/HCV-coinfected patients, smaller studies of boceprevir and telaprevir (plus PEG-IFN and ribavirin) have shown SVRs in the range of 60-75%, substantially higher than with standard therapy. These triple-therapy regimens, however, are complex and burdened with adverse effects and drug interactions.

Sofosbuvir

Sofosbuvir is an HCV polymerase inhibitor that was FDA approved in late 2013 for treatment of HCV in both HIV-coinfected and HCV-monoinfected patients with genotypes 1-4. It is approved for use with ribavirin alone (for genotypes 2 and 3) or with PEG-IFN + ribavirin (for most patients with genotypes 1 and 4), using specific protocols. It also is being studied in combination with other HCV medications, including in several interferon-free regimens. Use of sofosbuvir-containing regimens has resulted in very high SVR rates (80% to >90%) with 12 or 24 weeks of therapy, in both treatment-experienced and treatment-naive patients and in cirrhotic patients. Few significant drug-drug interactions with ARVs have been identified.

Simeprevir

Simeprevir is a HCV protease inhibitor that was FDA approved in late 2013 for treatment of genotype 1 HCV, in combination with PEG-IFN and ribavirin. Study data have shown SVR rates of 82% in treatment-naïve genotype 1 noncirrhotic patients and 58-65% in cirrhotic individuals treated with simeprevir + PEG-IFN + ribavirin. Among patients with the IL28B CC type, 95% achieved SVR. Simeprevir also is being studied in interferon-free regimens.

Simeprevir has markedly reduced efficacy in patients with the Q80K polymorphism, and screening for this is recommended before treatment. Simeprevir also has significant drug-drug interactions with some ARVs, in particular many protease inhibitors, nonnucleoside reverse transcriptase inhibitors, and the pharmacokinetic enhancer cobicistat.

Expansion of DAAs

In 2014-15, several additional HCV DAAs and combinations of DAAs are expected to be considered for FDA approval; many have the potential to be used in regimens that do not include interferon.

Treatment of acute HCV

As mentioned above, in the setting of acute HCV infection, RNA should be tested repeatedly for 12 weeks from the time of infection to ascertain whether spontaneous clearance will occur. If RNA is still present at 12 weeks, treatment should be offered.

With HIV/HCV-coinfected patients, as with HCV-monoinfected patients, early treatment of acute HCV infection yields a much higher rate of SVR than does treatment of chronic HCV infection. In three prospective trials of treatment for acute HCV in HIV-coinfected patients, using PEG-IFN + ribavirin for 24 or 48 weeks, the SVR for genotype 1 HCV was 55-75%, and 100% for genotype 3. By contrast, in the largest study of the same regimen for

chronic HCV treatment in HIV-coinfected patients (n = 868), the SVR was about 29% for genotype 1 and 62% for genotype 2 or 3. Currently, there are no data on the efficacy of DAAs to treat acute HCV infection in HIV-coinfected patients. Given the relatively high SVR rates that result from treatment of acute HCV with pegylated interferon and ribavirin, and the absence of data in this setting, it is not routinely recommended to use DAAs in acute coinfection at this time.

Treatment of chronic HCV

HIV coinfection is a strong indication for treatment of chronic HCV infection, because the risk of accelerated fibrosis and cirrhosis is higher for coinfecting patients. HIV-infected patients with low CD4 cell counts should not be excluded from HCV treatment on the basis of CD4 count alone; this is true particularly for patients already on ART. For timing of HCV treatment, see "Timing of HCV treatment and HIV treatment," below. Traditional treatment of chronic HCV infection in HIV/HCV-coinfected patients with PEG-IFN + ribavirin yields lower rates of SVR than does treatment of monoinfected patients (see above), but use of newer anti-HCV medications has improved the treatment outcomes in coinfecting patients.

Patients with a high risk of progression to cirrhosis, including coinfecting patients, should receive higher priority for treatment. Patients who have developed cirrhosis but remain compensated should be treated as soon as possible if they otherwise are candidates. Patients with decompensated liver disease should not receive HCV treatment (the likely risks of treatment outweigh potential benefits); appropriate candidates can be considered for liver transplantation. Many patients with minimal fibrosis may be best served by deferring treatment, pending availability of more effective and tolerable therapy options.

Current guidelines recommend treatment of HCV genotype-1-coinfected patients with PEG-IFN + ribavirin + an HCV protease

inhibitor for 48 weeks; because of potential drug interactions between HCV protease inhibitors and antiretroviral medications, the selection of HCV protease inhibitor and ARV drugs must be made with great care (see “Drug Interactions,” below). HCV genotypes 2-6 should be treated with PEG-IFN + ribavirin. However, as discussed above, the recent FDA approval of new DAA agents and the anticipated approval of others means that the paradigm for HCV treatment is in flux. It is anticipated that currently available and anticipated HCV drugs will be combined to construct a number of effective regimens (including all-oral and “interferon-free” regimens) that can be tailored to the treatment needs of particular patients. Based on current data, the emerging era of HCV treatment is expected to be one of higher response rates, lower side-effect profiles, and perhaps shorter courses of treatment.

To determine an appropriate treatment regimen, consultation with a specialist is recommended.

HCV Directly Acting Antivirals: Classes and Agents

FDA approved:

Protease Inhibitors (NS3/4a)

- Boceprevir
- Telaprevir
- Simeprevir

Nucleoside Polymerase Inhibitors:

- Sofosbuvir

Classes with Agents under Investigation

- Protease Inhibitors (NS3/4a)
- Nucleoside Polymerase Inhibitors
- NS5A Inhibitors
- Nonnucleoside Polymerase Inhibitors

Drug Interactions

HCV protease inhibitors and other DAAs may have significant interactions with certain HIV ARVs, particularly with protease inhibitors, nonnucleoside reverse transcriptase inhibitors, and the pharmacokinetic booster cobicistat. Interactions between many DAAs and ARVs have not been studied. Known and expected drug-drug interactions need to be carefully considered before selecting an HCV treatment regimen. Consult with HIV, HCV, and clinical pharmacy specialists. Table 2 shows potential DAA-ARV interactions, based on currently available data.

Table 2. Characteristics of Directly Acting Agents and Potential Interactions with ARVs

DAA	Mechanism	Activity Against HCV Genotype	Barrier to Resistance	Potential ARV Interactions
Telaprevir	NS3/4A protease inhibitor	1	Low	<ul style="list-style-type: none"> Contraindicated with all protease inhibitors except atazanavir/ritonavir Contraindicated with elvitegravir/cobicistat Requires increased dosage when administered with efavirenz No dosage adjustment when used with raltegravir
Boceprevir	NS3/4A protease inhibitor	1	Low	<ul style="list-style-type: none"> Contraindicated with all protease inhibitors, and with efavirenz and elvitegravir/cobicistat
Simeprevir	NS3/4A protease inhibitor	1, 2, 4, 5, 6	Low	<ul style="list-style-type: none"> Concentrations decreased by efavirenz, and may be decreased by etravirine and nevirapine; should not be given with these NNRTIs Concentrations increased by darunavir/ritonavir, ritonavir, and cobicistat; should not be given with any PI or cobicistat No clinically significant interactions with raltegravir, rilpivirine, tenofovir
Sofosbuvir	NS5B RNA polymerase inhibitor	1-6	High	<ul style="list-style-type: none"> Concentrations decreased by tipranavir/ritonavir No known clinically significant interactions with other ARVs

Adverse effects of treatment

IFN can cause fatigue, flulike symptoms, thrombocytopenia, nausea, depression, hair loss, weight changes, and many other potential side effects. IFN reduces total white blood cell counts, and can cause neutropenia. It also decreases CD4 cell counts, although the CD4 percentage usually does not change. IFN can reduce HIV RNA somewhat (by approximately 0.5 log₁₀ copies/mL).

Ribavirin can cause a hemolytic anemia, sore throat, cough, and other side effects. Zidovudine and didanosine should be avoided with patients taking ribavirin, because of the risk of compounded toxicities (anemia with zidovudine, neuropathy, lactic acidosis, liver toxicity, and pancreatitis with didanosine).

The side effects of boceprevir and telaprevir can include anemia, rash, and altered taste; telaprevir also can cause anorectal discomfort. The most commonly reported adverse effects of sofosbuvir + ribavirin regimens were fatigue, headache, insomnia, and nausea. In treatment arms containing sofosbuvir + PEG-IFN + ribavirin, side effects were similar to those reported with PEG-IFN + ribavirin, with the exception of increased rates of fatigue and nausea. The addition of simeprevir to PEG-IFN + ribavirin resulted in an increased incidence of rash including photosensitivity, pruritus, nausea, dyspnea, and hyperbilirubinemia.

HCV treatment should not be given during pregnancy, and women receiving HCV treatment should avoid pregnancy. IFN may cause fetal growth abnormalities, and

it is abortifacient in animals. Ribavirin is teratogenic, and both women and men must use two forms of contraception consistently during treatment with ribavirin and for 6 months after discontinuation of treatment. Boceprevir and telaprevir are FDA Pregnancy Category B drugs but must be used with PEG-IFN and ribavirin, which are not recommended.

Timing of HCV treatment and HIV treatment

The decision of whether and when to treat HCV among people infected with HIV must be made on an individual basis. When coinfecting patients require treatment for both infections, some experts begin with HIV treatment based on limited data that improved CD4 cell counts will enhance the response to HCV therapy, and this generally is recommended for patients with CD4 counts of <350 cells/ μ L. With patients who do not require ART urgently (e.g., because their CD4 counts are very high), consideration could be given to treating HCV first, with ART delayed until after completion of HCV treatment. This strategy is intended to simplify treatment and improve the tolerability of both therapies, though it brings the risk of HIV disease progression during HCV treatment. Patients already on ART generally should remain on ART throughout the course of HCV treatment, though regimens should be evaluated for adverse drug interactions with HCV drugs (e.g., with boceprevir and telaprevir). Consult with an HCV treatment expert to determine the appropriateness and timing of HCV treatment.

Some patients with HCV will experience worsening of hepatic function during ART, and liver function should be monitored closely. Some ARV medications are hepatotoxic and should be avoided or used cautiously; these include nevirapine, tipranavir, and high-dose ritonavir. Numerous other medications (e.g., fluconazole and isoniazid) are hepatotoxic and can pose problems for patients with impaired liver function.

Other care issues

Acute HAV or HBV infection in persons with chronic HCV can cause fulminant liver disease. All patients with HCV infection should be tested for immunity to HAV and HBV; patients who are not immune should be vaccinated.

Persons with HCV infection should be counseled to avoid exposure to hepatotoxins, including alcohol and hepatotoxic medications (e.g., acetaminophen in dosages >2 g per day, fluconazole, and isoniazid).

As appropriate, all persons with hepatitis C should receive individualized counseling on ways to reduce the risk of infecting others with HCV (including by unprotected sex, by sharing of injection drug equipment, other blood exposures [e.g., from sharing razors or tattoo equipment], and perinatal exposure).

Patient Education

- Advise patients that most people with HCV will be asymptomatic for many years and may never develop symptoms. However, slow progression of fibrosis can be happening in the absence of symptoms and can progress to cirrhosis, so ongoing monitoring is important.
- Patients can slow the development of fibrosis by avoiding alcohol and obesity, as fat in the liver can add to the liver damage.
- As with HIV, patients must avoid passing HCV to others. Emphasize the importance of safer sex to protect themselves as well as their partners. Instruct patients not to share toothbrushes, dental appliances, razors, sex toys, tattoo equipment, injection equipment, or personal care items that may have blood on them.
- Tell patients to discuss HCV with their sex partners and suggest that partners be tested for HCV.
- Women who are pregnant or considering pregnancy should talk with a specialist in HIV and HCV to discuss ways of decreasing the risk of perinatal transmission.
- HCV is not spread by coughing, sneezing, hugging, sharing food and water, or other casual contact.
- HAV can cause severe illness, liver damage, or even death in people with HCV. Patients who are not immune to HAV need to receive the two-part hepatitis A vaccination series.
- HBV can worsen liver function greatly if it is acquired in addition to HCV. Patients who are not immune to HBV need to receive the three-part hepatitis B vaccination series. If patients have been vaccinated in the past, they should have a blood test to confirm immunity.
- HCV treatment aims to clear the HCV virus from the body. That reduces risk of cirrhosis, end-stage liver disease, hepatocellular carcinoma, and liver-related death.
- HCV treatment is rapidly evolving and it is anticipated that several new regimens will be available over the next few years (2014-15). Each patient should talk to his or her health care provider about whether treatment is appropriate.
- Standard HCV treatment until 2011 included two drugs used together, pegylated interferon-alfa and ribavirin, for all patients being treated. In 2011, for genotype 1 patients, boceprevir or telaprevir became available to be used to create a triple-therapy regimen.
- In late 2013, simeprevir was FDA approved for use in combination with pegylated interferon and ribavirin for genotype 1 and 4 patients and sofosbuvir was approved for use in combination with pegylated interferon and ribavirin for genotype 1 patients and for use with ribavirin alone (interferon-free) in genotype 2 or 3 patients and some genotype 1 and 4 patients.
- Pegylated interferon can cause many side effects, including flulike symptoms, body aches, fevers, leukopenia, neuropathy, and depression. Most of these adverse effects are treatable with medications and resolve after therapy is completed.
- Ribavirin can cause side effects including rash, sore throat, and anemia.
- Multiple drug interactions are a concern for direct acting antivirals, including HIV medications. Drug-drug interactions need to be carefully considered before starting HCV treatment and choosing which HCV treatment is right for each patient.
- It is essential that both men and women who are taking ribavirin should use two forms of contraception consistently during ribavirin therapy and for 6 months after completion of treatment.

Herpes Simplex, Mucocutaneous

Background

Herpes simplex virus (HSV) types 1 and 2 cause both primary and recurrent oral and genital disease. HSV usually appears as a vesicular eruption of the mucous membranes of the oral or perioral area, vulva, perianal skin, rectum, and occasionally the inguinal or buttock areas. The eruption develops into tender or painful ulcerated lesions that frequently are covered with a clear yellow crust. In some patients, however, the typical painful vesicular or ulcerative lesions may be absent. Persons with HIV disease and low CD4 cell counts have more frequent recurrences of HSV and more extensive ulcerations than do HIV-uninfected people. Persistent HSV eruption (lasting >1 month) is an AIDS-indicator diagnosis. HSV facilitates HIV transmission.

S: Subjective

The patient may complain of eruption of red, painful vesicles or ulcers (“fever blisters”) with or without an exudate in the mouth, on the lips (and occasionally in nares), on the genitals, or in the perianal area. The patient may complain of burning, tingling, or itching before eruption of the lesions. In the genital area, symptoms may be nonspecific without any eruption of lesions; most HSV type 1 and 2 infections are asymptomatic, yet virus still can be shed.

The vesicles will rupture and ulcerate, generally crusting over and healing in approximately 7-14 days. The lesions may be pruritic and are often painful. As immunosuppression progresses, the lesions may recur more frequently, grow larger or coalesce, and become chronic and nonhealing.

Perform a history, asking the patient about the symptoms described above, duration, associated symptoms, and history of oral or genital HSV infection.

O: Objective

Look for grouped vesicular or ulcerative lesions on an erythematous base on the mouth, anus, or external genitals, or ones that are visible on speculum or anoscopic examination. When immunosuppression is severe, lesions may coalesce into large, painful, and nonhealing

ulcerations that spread to the skin of the thighs, lips, face, or perirectal region. These chronic erosive lesions may be confused with a chronic bacterial infection or decubitus ulcer, and should prompt consideration of acyclovir-resistant HSV infection. Recurrent lesions may start atypically, first appearing as a fissure, pustule, or abrasion.

A: Assessment

A partial differential diagnosis includes the following:

- Oral: Oral aphthous ulcers
- Genital: Chancroid, syphilis, cytomegalovirus, candidiasis, drug-related eruption, trauma

P: Plan

Diagnostic Evaluation

A clinical diagnosis of HSV can be made on the basis of the patient’s symptoms and clinical appearance only if vesicles and constitutional symptoms are present, but symptoms and signs may be variable, and primary syphilis always must be ruled out. Also, HSV-1 (rather than HSV-2) is increasingly the cause of initial episodes of anogenital herpes. For these reasons, current guidelines recommend laboratory testing to establish the diagnosis of HSV and to determine its type.

For cell culture or polymerase chain reaction (PCR), obtain a specimen from a freshly opened vesicle or the base of an ulcer for culture confirmation. Note that lesions that are >72 hours old or are beginning to resolve may not show HSV in culture. Tzanck smears are not sensitive or specific.

PCR is more sensitive for detection of herpes DNA in ulcerative lesions, but is more expensive to perform and is less widely available than viral culture. If virologic test results are positive, typing should be performed to determine the type of HSV. Negative results do not rule out the possibility of HSV infection.

If cultures are negative, a sample can be taken from a fresh lesion for another culture or for PCR. In addition, type-specific serologic tests may be useful in the evaluation of symptomatic patients in whom a diagnosis of genital HSV is not clear. Current sexually transmitted disease (STD) guidelines also recommend that serologic testing be considered for HIV-infected individuals, for MSM at risk of HIV infection, and for those who present for STD evaluation if there is no history of past genital HSV diagnosis. Glycoprotein G (gG)-based serologic assays are recommended, as older assays do not reliably differentiate HSV-1 antibody from HSV-2 antibody.

In any patient who presents with genital, anal, or oral ulceration, even if the suspicion of HSV is high, syphilis serologic testing (rapid plasma reagin [RPR], Venereal Disease Research Laboratory [VDRL], enzyme immunoassay [EIA], or chemiluminescent immunoassay [CIA]) should be done (see chapter *Syphilis*).

Treatment

Empiric antiviral treatment for new-onset suspicious lesions may be initiated in the absence of laboratory confirmation, especially if symptoms are significant. Dosage reduction of the antivirals is required for patients with renal impairment.

Note: treatment recommendations reflect current CDC/NIH/IDSA opportunistic infections guidelines; the CDC STD guideline recommendations are slightly different (see “References,” below).

Orolabial lesions (5-10 days) or genital lesions (5-14 days)

- Valacyclovir 1,000 mg PO BID
- Famciclovir 500 mg PO BID
- Acyclovir 400 mg PO TID

Severe mucocutaneous HSV disease

Treat initially with acyclovir 5 mg/kg IV Q8H until the lesions have started to regress, then an oral HSV antiviral agent (as above) until all lesions have healed.

Suppressive therapy

Consider suppressive therapy for patients with frequent or severe recurrences and those with HSV-2. Treatment may be continued indefinitely. If acyclovir is used, its dosage may need to be increased to 800 mg BID or TID for individuals whose HSV episodes are not adequately suppressed by 400 mg BID. Suppressive therapy using valacyclovir reduces the risk of HSV transmission between HIV-uninfected heterosexual partners but the extent to which this is true in HIV-infected persons is unknown. Effective antiretroviral therapy (ART) also may reduce the frequency of HSV outbreaks.

- Valacyclovir 500 mg PO BID
- Famciclovir 500 mg PO BID
- Acyclovir 400 mg PO BID

Acyclovir-resistant HSV

The diagnosis of acyclovir-resistant HSV should be suspected if lesions fail to respond to 7-10 days of standard therapy and should be confirmed with culture and sensitivities. Cross-resistance to valacyclovir and ganciclovir will be present, and cross-resistance to famciclovir is likely. The usual alternative treatment is foscarnet (40 mg/kg IV Q8H); other possibilities include IV cidofovir, topical imiquimod, topical trifluridine, and topical cidofovir. An infectious disease or HIV specialist should be consulted.

HSV During Pregnancy

Acyclovir appears to be safe and effective for use by pregnant women and remains the drug of choice. Few data are available on the use of valacyclovir and famciclovir during pregnancy but they appear to be safe.

It is important to avoid peripartum transmission of HSV. For women with recurrent or new genital HSV late in pregnancy, obstetric or infectious disease specialists should be consulted, and suppressive therapy with valacyclovir or acyclovir is recommended. All women should be evaluated carefully for symptoms and signs of genital HSV at delivery.

Patient Education

- Patients should be told that HSV has no cure, but treatment can decrease symptoms and recurrences. Treatment also has been shown to decrease shedding and HSV transmission in HIV-uninfected discordant couples, but it has not been studied in HIV-infected couples. Outbreaks and viral shedding may occur at intervals for the rest of their lives but frequency generally decreases with age of infection.
- HSV may be spread through kissing (if mouth or lips are infected) and sexual contact (oral, anal, or vaginal). Most HSV is transmitted when no genital lesions are present, so it is important that patients inform their sex partners of their herpes infection before sexual activity. Patients must avoid all sexual contact when lesions are visible, because a high volume of virus is present at those times. Correct use of condoms at each sexual encounter reduces the risk of HSV transmission.
- All patients with genital HSV should be encouraged to inform their partners.
- Episodic treatment is most effective when taken early in the outbreak, so patients not taking suppressive therapy should keep medication on hand and start treatment at the first signs of a prodrome or eruption.
- Genital HSV in a pregnant woman around the time of delivery can cause severe illness in the newborn. Women should inform their obstetrician and pediatrician if they have a history of HSV or are exposed to or infected with HSV during pregnancy. Pregnant women who do not have HSV should avoid sexual practices that facilitate HSV transmission in the third trimester with partners who have HSV, and men who have HSV should avoid sexual practices that facilitate HSV transmission with pregnant women in their third trimester who do not have HSV.

Herpes Zoster/Shingles

Background

Shingles is a skin or mucosal infection caused by the varicella-zoster virus (VZV) that occurs along a dermatome and represents a reactivation of varicella (chickenpox). Zoster is common in patients with HIV infection, including apparently healthy individuals before the onset of other HIV-related symptoms. The incidence may be higher among patients with low CD4 cell counts and during the 4 months after initiating potent antiretroviral therapy.

Zoster may be particularly painful or necrotic in HIV-infected individuals. Disseminated infection, defined as outbreaks with >20 vesicles outside the primary and immediately adjacent dermatomes, usually involves the skin and the visceral organs. Neurologic complications of zoster include encephalitis, aseptic meningitis, cranial nerve palsies, optic neuritis, transverse myelitis, and vasculitic stroke.

S: Subjective

The patient complains of painful skin blisters or ulcerations along one side of the face or body. Loss of vision may accompany the appearance of facial lesions. Pain in a dermatomal distribution may precede the appearance of lesions by many days (prodrome).

Assess the following during the history:

- Duration of pain or blisters (average of 2-3 weeks if untreated)
- Location of pain or blisters; severity of pain
- History of chickenpox (usually in childhood)

O: Objective

Perform a skin and neurologic examination to include the following:

- Vesicular lesions with erythematous bases in a dermatomal distribution; may be bullous or hemorrhagic
- Necrotic lesions; may persist for as long as 6 weeks
- Dermatomal scarring (particularly in dark-skinned individuals)
- Lesions in the eye area or tip of nose,

along the trigeminal nerve; these represent ophthalmic nerve involvement, which requires immediate evaluation and IV treatment (see below)

A: Assessment

- Rule out other causes of vesicular skin eruptions (e.g., herpes simplex virus, severe drug reactions).
- Assess contact exposures (see below).

P: Plan

Diagnostic Evaluation

The diagnosis usually is clinical and is based on the characteristic appearance and distribution of lesions. If the diagnosis is uncertain, perform viral cultures or direct fluorescent antigen or polymerase chain reaction test of samples from a freshly opened vesicle or biopsy from the border of a lesion.

Treatment

- Treatment ideally should begin within 72 hours of an outbreak or while lesions are not yet fully crusted and should be continued for 7-10 days. Early treatment may attenuate a herpes zoster attack.

Localized dermatomal zoster

• Preferred therapy

- Valacyclovir 1 g PO TID
- Famciclovir 500 mg PO TID

• Alternative therapy

- Acyclovir 800 mg PO 5 times daily
- Dosage reductions of these drugs are required for patients with renal impairment.
- If new blisters are still appearing at the end of treatment, repeat course of PO therapy or consider IV treatment. Adjunctive corticosteroids aimed at preventing postherpetic neuralgia are not recommended.
- Consult an ophthalmologist immediately if lesions appear in the eye area or on the tip of the nose, or if the patient complains of visual disturbances, because VZV-related retinal necrosis can cause blindness. Because of the rapid progression associated with this diagnosis, hospitalization for administration of IV acyclovir and possibly foscarnet is recommended.
- VZV from zoster lesions is contagious, and contact or airborne spread from vesicle fluid may cause chickenpox in nonimmune people. If a zoster patient's household includes a pregnant woman (HIV infected or uninfected) or an HIV-infected child, consult with a specialist immediately for advice on management of exposed household members. (See "Postcontact Chickenpox Prevention," below.)
- Give analgesics for pain; narcotics may be required.
- Postherpetic neuralgia (PHN) is a common sequela of zoster. Antiviral therapy may reduce the risk of PHN, but PHN often requires special treatment for pain control. Treatment options include:
 - Nortriptyline 10-25 mg. To be taken at bedtime and increased by 25 mg every 3-5 days to a maximum dosage of 150 mg QD

until pain is controlled, assuming adverse effects remain tolerable. Other tricyclics may be used.

- Gabapentin 100-300 mg PO BID; this may be increased by 300 mg every 3 days until reaching 3,600 mg total daily dosage. Adjust gabapentin dosage in patients with kidney disease.
- Pregabalin 75 mg BID (or 50 mg TID) in patients with estimated creatinine clearance of >60 mL/minute; this may be increased to 300 mg total daily dosage over the course of a week as needed.
- Lidocaine 5% patches provide good local relief with minimal systemic absorption. Up to 3 patches may be applied simultaneously to the affected area for up to 12 hours in a 24-hour period.
- Capsaicin cream may be applied to the affected area TID or QID. Patients should wear gloves to apply the cream and wash their hands with soap and water afterward.
- Sustained-release opiates may be required.

(See chapter *Pain Syndrome and Peripheral Neuropathy* for more options and specific recommendations.)

Severe or unresponsive cases

- IV acyclovir may be indicated if:
 - The patient is severely immunocompromised
 - The ophthalmic branch of the trigeminal nerve is affected (as noted above)
 - Dissemination has occurred; visceral disease is suspected
 - Lesions are extensive
 - Lesions are not responsive to oral therapy
 - Pain is intractable in the setting of active skin lesions
- The usual adult dosage is 10-15 mg/kg Q8H for 7-14 days based on clinical response; can switch to oral therapy when signs/symptoms are improving. Dosage reduction is required

for patients with renal impairment. Refer to an infectious disease specialist.

- Acyclovir resistance may occur in patients previously treated with acyclovir or related drugs, and foscarnet may be required for effective treatment. Resistance should be suspected if lesions are not resolving after 10 days of therapy or if they develop an atypical appearance. Such lesions should be cultured and drug sensitivities should be obtained.

Prevention

The vaccine for prevention of herpes zoster (Zostavax) has not been recommended by national guidelines for use in persons with HIV infection. Limited data in HIV-infected individuals with CD4 counts of >200 cells/ μL show safety and immunogenicity. The zoster vaccination may be considered for select patients >50 years of age with CD4 counts of >200 cells/ μL who have evidence of varicella immunity (if they have no evidence of varicella immunity, give the primary varicella vaccination). The vaccine is contraindicated in persons with AIDS or clinical manifestations of HIV.

Postcontact Chickenpox Prevention

All HIV-infected susceptible persons, including pregnant women, who have close contact with a patient who has chickenpox or zoster must be treated to prevent chickenpox. Exposed individuals who have no history of chickenpox or shingles or no detectable antibody against VZV should be administered varicella-zoster immune globulin (VariZIG) as soon as possible, but at least within 10 days after contact. Some experts also would

recommend varicella vaccination for exposed patients with CD4 counts of ≥ 200 cells/ μL , or preemptive treatment with acyclovir or valacyclovir; these approaches have not been studied in HIV-infected persons. Even immunocompetent adults with primary VZV (chickenpox) can develop viral dissemination to the visceral organs. HIV-infected patients may develop encephalitis, pneumonia, or polyradiculopathy during primary varicella (chickenpox) or reactivated zoster (shingles).

Patient Education

- Patients should bathe the skin lesions in mild soap and water. For necrotic lesions, use warm, moist compresses 2-3 times a day to remove debris.
- Antibiotic ointments may help prevent secondary infection and keep dressings from sticking.
- Advise patients to take their medications as directed, and to contact the clinic if symptoms worsen.

Histoplasmosis

Background

Histoplasmosis is caused by *Histoplasma capsulatum*, a fungus that thrives in soil contaminated by droppings from birds and bats. In the United States, *H. capsulatum* is found most often along the Ohio and Mississippi River Valleys, in the central, mid-Atlantic, and south-central states, and from Alabama to southwest Texas. In highly prevalent areas, such as Indianapolis and Kansas City, more than 80% of the population has been exposed to *Histoplasma* through inhalation of airborne infectious elements. Histoplasmosis also is found in the Canadian provinces of Quebec and Ontario, Puerto Rico, Mexico, Central and South America, Africa, East Asia, and Australia.

The initial infection in most cases either produces no symptoms or manifests only as a mild flulike illness. However, immunosuppressed individuals may develop disseminated disease. Progressive disseminated histoplasmosis often represents a reactivation of latent infection, occurs late in the course of HIV disease (the CD4 count usually is <150 cells/ μ L), and is an AIDS-defining illness. Pulmonary histoplasmosis (without dissemination) may occur in people with higher CD4 counts. Within endemic areas, histoplasmosis accounts for 5% of opportunistic infections among patients with AIDS. In hyperendemic areas, the prevalence of histoplasmosis may reach 25% among AIDS patients. The incidence of histoplasmosis in the United States has declined with the use of effective antiretroviral therapy (ART).

Common clinical features that may be associated with histoplasmosis are shown in Table 1.

S: Subjective

Histoplasmosis may be difficult to diagnose because the symptoms are nonspecific. In addition, clinicians may not consider this diagnosis in low-prevalence areas.

Patients may experience fever, weight loss, fatigue, cough, and shortness of breath. They also may develop skin lesions, adenopathy, central nervous system (CNS) changes, oropharyngeal ulcers, nausea, diarrhea, and abdominal pain. Symptoms usually begin several weeks before patients present for care. On occasion, histoplasmosis presents abruptly as a sepsis-like syndrome.

Ask the patient about possible exposures, but note that absence of reported exposures does not rule out histoplasmosis. The following are associated with significant risk of exposure:

- Residence or travel in endemic areas (see above); in the United States, particularly the Ohio and Mississippi River Valleys
- Occupational history of farming or construction/remodeling
- Hobbies that involve contact with caves, bird roosts or nests, or farm areas
- Contact with soil having a high organic content and undisturbed bird droppings, such as that found around old chicken coops and bird roosts

Table 1. Common Clinical Manifestations of Histoplasmosis

Symptom Group	Percentage of Cases	Examples
Constitutional	95%	<ul style="list-style-type: none"> • Weight loss • Fatigue • Fever
Gastrointestinal	>10%	<ul style="list-style-type: none"> • Splenomegaly • Diarrhea • Hepatomegaly • Abdominal pain
Respiratory	50-60%	<ul style="list-style-type: none"> • Pneumonia • Pneumonitis
Hematologic	>50%	<ul style="list-style-type: none"> • Anemia • Thrombocytopenia • Leukopenia
Neurologic	15-20%	<ul style="list-style-type: none"> • Meningitis, cerebritis • Focal parenchymal lesions • Encephalopathy
Septic	10-20%	<ul style="list-style-type: none"> • Hypotension • Disseminated intravascular coagulopathy • Respiratory insufficiency • High fever • Renal or hepatic failure
Dermatologic	<10%	<ul style="list-style-type: none"> • Follicular, pustular, maculopapular, or erythematous lesions

O: Objective

Measure vital signs and document fever.

Perform a complete physical examination, with special attention to the lymph nodes, lungs, abdomen, skin, and neurologic system.

Common findings include enlargement of the liver, spleen, and lymph nodes. Skin lesions and oropharyngeal ulcers may be seen.

A: Assessment

A partial differential diagnosis includes the following:

- Other deep-seated fungal infections, such as cryptococcosis and coccidioidomycosis
- Mycobacterial disease (*Mycobacterium tuberculosis* or *Mycobacterium avium* complex)
- *Pneumocystis* pneumonia
- Lymphoma

P: Plan

Diagnostic Evaluation

- The *H. capsulatum* antigen test is sensitive and specific. The test is most sensitive for urine samples (>95% in disseminated disease), but can be used on serum (>85% sensitive in disseminated disease), bronchial fluids, or cerebrospinal fluid (CSF) specimens. Results may be obtained in a few days' time. Urine antigen levels can be used to monitor the response to therapy.
- Cultures of blood, bone marrow, and specimens from other sources have reasonable sensitivity (about 85%), but obtaining results may take several weeks.
- Wright stain of the buffy coat of a blood specimen may reveal intracellular organisms.
- Biopsies of lymph nodes, liver, cutaneous lesions, and lungs may be diagnostic in up to 50% of cases; bone marrow can be stained with methenamine silver to show the organism within macrophages.

- Meningitis can be challenging to diagnose. Diagnostically, *Histoplasma* antigen or anti-*Histoplasma* antibodies can be detected in CSF in up to 70% of cases, whereas results for cultures are often negative. Nonspecific findings in the CSF include elevated protein and low glucose as well as a lymphocytic pleocytosis. A diagnosis of *Histoplasma* meningitis should be considered if the patient has known disseminated disease and other more common etiologies of meningitis have been ruled out.
- Lactate dehydrogenase (LDH) and ferritin, although not specific, may be markedly elevated in disseminated disease.
- Complete blood count and chemistry panels may show pancytopenia, elevated creatinine, or abnormal liver function.

Treatment

Treatment consists of two phases: induction and chronic maintenance. Treatment should be continued for at least 12 months.

Severe disseminated histoplasmosis

Severe infection requires IV induction therapy with a lipid formulation of amphotericin; standard amphotericin is less effective and is associated with more adverse effects, but may be used as an alternative.

- **Induction therapy (≥2 weeks or clinically improved):**
 - **Preferred:** Liposomal amphotericin B lipid formulation 3 mg/kg IV QD
 - **Alternatives:** Amphotericin B lipid complex or amphotericin B cholesteryl sulfate complex 3 mg/kg IV QD
- **Maintenance therapy:** After ≥2 weeks of therapy or improvement of the patient's clinical status, therapy may be switched to itraconazole 200 mg PO TID for 3 days, then BID for at least 12 months of therapy. Liquid formulation of itraconazole is preferred.

Histoplasma meningitis

Amphotericin B must be used because itraconazole has poor penetration into the CNS:

- **Induction therapy:** Liposomal amphotericin B 5 mg/kg QD for 4-6 weeks
- **Maintenance therapy:** Itraconazole 200 mg PO BID or TID for ≥12 months and until abnormal CSF findings resolve

Mild to moderate disseminated histoplasmosis without CNS involvement

- **Induction and maintenance therapy:** Itraconazole 200 mg PO TID for 3 days followed by itraconazole 200 mg BID for ≥12 months; liquid formulation of itraconazole is preferred

Pulmonary histoplasmosis in patients with CD4 counts of >300 cells/μL

Manage as for non-immunocompromised patients.

See "Potential ARV Interactions," below, regarding azoles.

Long-term suppressive therapy

Long-term therapy must be given to prevent relapse after 12 months of initial treatment; preferred therapy consists of itraconazole 200 mg PO QD. Fluconazole 800 mg QD is less effective but can be used as an alternative for patients who cannot tolerate or cannot obtain itraconazole. Voriconazole and posaconazole appear to be effective. (See "Potential ARV Interactions," below, regarding azoles.)

Few data support the discontinuation of chronic maintenance therapy. One small study sponsored by the AIDS Clinical Trials Group demonstrated safety in discontinuing suppressive itraconazole therapy for patients who met the following criteria: had completed >1 year of itraconazole therapy, negative blood cultures, *Histoplasma* serum antigen <2 units, CD4 counts >150 cells/μL, and had been on ART for ≥6 months. Therefore, per U.S. Centers for Disease Control and Prevention guidelines, discontinuing

suppressive therapy for any patient who meets these criteria can be considered. Suppressive therapy should be restarted if the CD4 count drops to <150 cells/ μ L.

Monitoring and relapse

Monitor either serum or urine *Histoplasma* antigen, as well as clinical status, to evaluate response to therapy; a rise in the antigen level suggests relapse of histoplasmosis. A drug level of itraconazole should be measured at least once after 2 weeks of therapy as absorption of this drug can be erratic and interactions are expected between itraconazole and some ARVs.

In cases of treatment failure, both voriconazole and posaconazole have been successful in a few case reports; if treatment failure is suspected, an infectious disease specialist should be consulted.

Primary Prophylaxis

Currently, there are no studies that prove any survival benefit in using primary prophylaxis; however, prophylaxis with itraconazole 200 mg PO QD can be considered for high-risk patients whose CD4 counts are <150 cells/ μ L (e.g., those with occupational exposure and those who reside in hyperendemic regions). HIV-infected patients with CD4 counts of <150 cells/ μ L should be educated about avoiding exposure.

Primary prophylaxis can be discontinued if the CD4 count remains \geq 150 cells/ μ L for 6 months on effective ART; prophylaxis should be restarted if the CD4 count drops to <150 cells/ μ L.

Potential ARV Interactions

There may be significant drug-drug interactions between certain systemic antifungals, (particularly itraconazole, voriconazole, and posaconazole) and ritonavir-boosted protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), elvitegravir/cobicistat, or maraviroc. Some combinations are contraindicated and others require dosage adjustment of the ARV, the antifungal, or both, and/or monitoring of drug levels. Check for adverse drug interactions before prescribing. See relevant tables in the U.S. Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, or consult with an expert.

Patient Education

- Histoplasmosis is not transmitted from person to person, so isolation is not necessary.
- Patients should take all their medications exactly as prescribed by their health care provider.
- Even with maintenance therapy, relapses can occur. Patients should contact their provider immediately if symptoms worsen.
- Persons with histoplasmosis should be treated with antiretroviral therapy.
- The azoles may cause birth defects. Women who are taking azole medications should avoid pregnancy. In addition, itraconazole and other azoles interact with some antiretrovirals and other medications; patients should tell their provider if they begin taking any new medications while receiving itraconazole.

Kaposi Sarcoma

Background

Kaposi sarcoma (KS) is an endothelial neoplasm that usually occurs as skin or oral lesions but may involve the internal organs. It is the most common AIDS-associated neoplasm and is an AIDS-defining disease. AIDS-associated KS is one of four types of KS, along with classic, endemic, and organ transplant-associated KS. Although the types vary in epidemiology and clinical presentation, all are associated with human herpesvirus type 8 (HHV-8), also known as KS-associated herpesvirus. The clinical manifestations of AIDS-associated KS (sometimes called epidemic KS) range in severity from mild to life-threatening. The progression of disease may be rapid or slow, but the overall prognosis is poor in the absence of treatment. The skin lesions of KS, even when they do not cause medical morbidity, may cause significant disfigurement and emotional distress.

AIDS-associated KS usually occurs in HIV-infected persons with advanced immunosuppression (CD4 count of <200 cells/ μL), but may occur at any CD4 count. In the United States and Europe, KS occurs in all HIV risk groups, but most frequently among men who have sex with men (MSM). Risk factors for MSM include multiple sexual partners and a history of sexually transmitted diseases (STDs); risk factors for other groups have not been clearly identified. The transmission of HHV-8 is not well understood. Although experts believe HHV-8 is transmitted sexually, it apparently also passes from person to person by other routes.

The incidence of KS in resource-abundant countries has declined markedly since the early 1990s, in part because of the widespread availability of effective combination antiretroviral therapy (ART). In parts of sub-Saharan Africa, where endemic KS has long existed in people with normal immune function, the incidence of KS has risen sharply in people with HIV. ART appears to be effective in reducing the risk of AIDS-associated KS, particularly when initiated before the development of advanced immunosuppression.

S: Subjective

Skin Lesions

The cutaneous presentation of KS is the most common, occurring in 95% of cases. Lesions may occur anywhere on the skin. Common sites include the face (particularly under the eyes and on the tip of the nose), behind the ears, and on the extremities and torso. Lesions may be macules, papules, plaques, or nodules. At first, the lesions are small and may be flat. Their color may vary from pink or red to purple or brown-black (the latter particularly in dark-skinned individuals), and they are nonblanching, nonpruritic, and painless (lesions may become painful in the setting of immune reconstitution inflammatory

syndrome [IRIS] associated with KS). Over time, the lesions often increase in size and number, darken, and rise from the surface; they may progress to tumor plaques (e.g., on the thighs or soles of the feet), or to exophytic tumor masses, which can cause bleeding, necrosis, and extreme pain.

Oral Lesions

Oral lesions may be flat or nodular and are red or purplish. They usually appear on the hard palate, but may develop on the soft palate, gums, tongue, and elsewhere. Oral lesions, if extensive, may cause tooth loss, pain, and ulceration.

Lymphedema

Lymphedema associated with KS usually appears in patients with visible cutaneous lesions, and edema may be out of proportion to the extent of visible lesions. Lymphedema also may occur in patients with no visible skin lesions. Common sites include the face, neck, external genitals, and lower extremities. A contiguous area of skin usually is involved. Lymph nodes may be enlarged.

Pulmonary KS

Pulmonary KS may be asymptomatic or cause intractable cough, bronchospasm, hemoptysis, chest pain, and dyspnea. The patient may exhibit difficulty breathing, bronchospasm, cough (sometimes with hemoptysis), and hypoxemia.

Gastrointestinal KS

Gastrointestinal KS may arise anywhere in the gastrointestinal tract. Patients usually are asymptomatic except in cases of intestinal obstruction or bleeding. KS may cause protein-losing enteropathy. Visceral disease is uncommon in the absence of extensive cutaneous disease.

During the history, ask about the symptoms noted above and associated characteristics, including the following:

- Duration of lesions
- Pain
- Frequency of new lesions
- Respiratory or gastrointestinal symptoms
- Edema or swelling

O: Objective

Physical Examination

Perform a careful physical examination, with particular attention to the following:

- Vital signs
- Skin (examine the entire skin surface including the scalp and conjunctiva)
- Oropharynx
- Extremities and external genitals (look for lesions, edema)
- Lymph nodes

Examine the lungs, abdomen, rectum, and other systems as indicated.

A: Assessment

The partial differential diagnosis depends on the type of symptoms present.

For cutaneous, oral, and lymph node presentations, consider the following:

- Bacillary angiomatosis
- Lymphoma
- Dermatofibromas
- Bacterial or fungal skin infections
- Venous stasis

For pulmonary symptoms, consider the following:

- *Pneumocystis jiroveci* pneumonia (PCP)
- Cytomegalovirus (CMV) pneumonia
- Pulmonary lymphoma (rare)

P: Plan

Diagnostic Evaluation

For cutaneous or oral KS, the diagnosis often is suggested by the appearance of skin or mucous membrane lesions. Biopsy of a lesion (or a suspect lymph node) is required to verify the diagnosis and rule out infectious or other neoplastic causes. Biopsy is particularly

important if the lesions are unusual in appearance or if the patient has systemic or atypical symptoms.

If respiratory symptoms are present, obtain chest X-rays or computed tomography (CT) studies. The chest X-ray typically shows diffuse interstitial infiltrates, often accompanied by nodules or pleural effusion. Radiographic findings may be suggestive of KS, but cannot provide a definitive diagnosis. Bronchoscopy with visualization of characteristic endobronchial lesions usually is adequate for diagnosis.

For patients with gastrointestinal symptoms and suspected KS, perform endoscopy.

If the patient has fever or respiratory, gastrointestinal, or constitutional symptoms, evaluate for other infectious and malignant causes (e.g., by culture or biopsy) as suggested by the history and physical examination.

Treatment

Treatment of KS is not considered curative, and no single therapy is completely efficacious. ART is a key component of the treatment of KS and should be initiated promptly (or optimized to achieve complete HIV RNA suppression) for all persons with KS (for further information, see chapter *Antiretroviral Therapy*). KS often regresses and sometimes resolves in patients treated with effective ART. Some data suggest that protease inhibitors may have an anti-KS effect; however, non-PI-containing regimens also lead to KS regression; the role of specific antiretroviral agents beyond HIV control in KS remains unclear.

KS-associated IRIS has been described, and patients may experience painful enlarged lesions or progression of KS lesions during the first months of ART; they should be advised of this possibility.

Specific treatment of KS depends on various factors such as the number, extent, severity, and location of lesions; cosmetic considerations; and presence of visceral

involvement. The goals of therapy may vary according to the clinical presentation and may include controlling symptoms, improving cosmetic appearance, reducing edema, eliminating pain, and clearing lesions. ART alone may be effective in mild-to-moderate KS. Local treatment (in conjunction with ART) may be given to patients who have bothersome symptoms from a few small lesions. Systemic therapy (in conjunction with ART) is needed for more extensive or more severe disease, including symptomatic visceral disease, widespread skin involvement, significant edema, and rapidly progressive KS. Consultation with a KS-experienced oncologist or dermatologist is recommended.

Local treatment of limited disease

Options for local treatment of limited disease include the following:

- ART with observation for response (limited, stable cutaneous disease may require no specific treatment)
- Intralesional chemotherapy (e.g., vinblastine)
- Radiation therapy, for localized or facial lesions (may cause mucositis when used for oropharyngeal lesions)
- Cryotherapy
- Laser therapy

Treatment of extensive or rapidly progressing disease

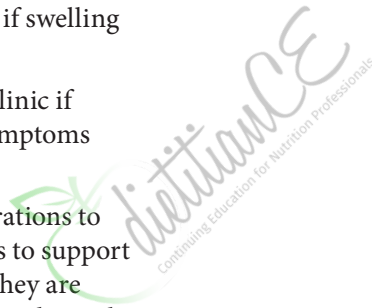
Extensive or rapidly progressing disease may include lymphedema, intraoral or pharyngeal disease that interferes with eating, painful or bulky lesions, and symptomatic pulmonary or visceral disease. Options for treatment include the following:

- Intralesional chemotherapy (e.g., vinblastine)
- Systemic chemotherapy (e.g., liposomal formulations of doxorubicin or daunorubicin, or paclitaxel)

- Numerous experimental agents are under evaluation
- Consultation with an oncologist is recommended for optimal treatment of extensive disease

Patient Education

- KS often responds to treatment. Educate patients that ART is a cornerstone of treatment; encourage them to start and adhere to ART.
- Swollen or edematous lesions increase the risk of cellulitis, whereupon lesions can become infected and progress rapidly. Advise patients to avoid injuring swollen or edematous lesions, to keep them clean, and to call their health care provider if lesions appear to be spreading or if swelling worsens.
- Advise patients to return to the clinic if respiratory or gastrointestinal symptoms develop.
- Patients may use cosmetic preparations to cover facial lesions. Refer patients to support groups or counseling services if they are having difficulty coping with their physical appearance.



Molluscum Contagiosum

Background

Molluscum contagiosum is a viral infection of human epidermal keratinocytes, caused by a double-stranded DNA virus of the Poxviridae family. Molluscum appears as papules or nodules and sometimes is called “molluscum warts.” It is seen most frequently in HIV-uninfected children (up to 5% of children in the United States), in sexually active young adults, and in immunocompromised persons. It occurs in 5-18% of HIV-infected persons. Molluscum is benign but may cause extensive and cosmetically bothersome lesions, particularly in persons with advanced HIV infection.

Transmission occurs by person-to-person skin-to-skin contact (e.g., sexual activity, contact sports [especially wrestling], or simply touching) or via fomites (towels, bedclothes, clothing [including underwear], soft toys, shaving utensils, electrolysis equipment, tattooing tools, and sponges). The virus may be spread to other areas via self-inoculation (e.g., scratching, shaving, or touching a lesion).

In immunocompetent persons, the infection usually resolves spontaneously after 6-12 months, though genital lesions may remain longer. In HIV-infected persons, the lesions may be more extensive and persistent. There is a strong correlation between the degree of immunosuppression and the risk of molluscum infection, the number of lesions, and the ability of lesions to resist treatment.

S: Subjective

Patients complain of new papules on the trunk, axillae, antecubital and popliteal fossae, face, or genital/crural area. Papules of molluscum contagiosum may cause no symptoms but also can be intensely pruritic or tender to the touch. Ask patients whether others in the home (especially children and adolescents) or their sex partners have similar papules. Genital lesions are transmitted sexually; patients may recall seeing such lesions on the genitals of a previous partner.

Ask about fever or other systemic symptoms to evaluate for other causes of the papules.

O: Objective

Perform a thorough evaluation of the skin, genitals, and mouth. Molluscum commonly presents as multiple grouped lesions. The lesions are white, pink, or flesh colored; shiny, smooth surfaced, firm, pearly, and spherical (dome-shaped) papules (2-5 mm) or nodules (6-10 mm), with umbilicated, or dimpled, centers. Patients with HIV infection may develop giant lesions (>1 cm) or clusters of hundreds of small lesions. Occasionally, molluscum will have a polyp-like appearance. Lesions are usually found on the head, face, or neck or in the genital area, but may affect every part of the body except the palms and soles. Molluscum may occur inside the mouth, vagina, and rectum, and around the eyes. Lesions on the eyelids can cause conjunctivitis.

A: Assessment

A partial differential diagnosis includes the following:

- Disseminated cryptococcosis
- Histoplasmosis skin lesions
- *Penicillium marneffei*
- Other fungal skin lesions
- Folliculitis
- Syphilis, condyloma acuminata, vulvar syringoma for multiple small molluscum genital lesions
- Squamous or basal cell carcinoma

P: Plan

Diagnostic Evaluation

The diagnosis of molluscum usually is based on the characteristic appearance of the lesions. Perform histologic or other laboratory testing to confirm the diagnosis or to exclude other infections or malignancies. Special staining will show keratinocytes containing eosinophilic cytoplasmic inclusion bodies. Electron microscopy will show poxvirus particles.

Treatment

Because molluscum does not cause illness and rarely causes symptoms, the treatment usually is undertaken primarily for cosmetic purposes. For individuals with large or extensive lesions, molluscum may be disfiguring or stigmatizing, and treatment may be important for their well-being. Treatment (particularly of genital lesions) can be considered in order to prevent transmission to others.

In HIV-infected patients, molluscum is difficult to eradicate and lesions often recur, particularly if immune suppression persists. Effective antiretroviral therapy may achieve resolution of lesions or significant improvement in the extent or appearance of molluscum and should be recommended for all.

Lesions that remain after weeks of antiretroviral therapy should be treated to prevent further spread. Refer complex cases to a dermatologist.

Choice of treatment modality is based on age, likelihood of compliance, number and size of lesions, and potential adverse effects of treatment. Therapeutic options include the following:

- **Local excision:** May be done by curettage, cryotherapy, electrocautery, or evisceration. Adverse effects include pain, irritation, soreness, and mild scarring. Repeated treatments are necessary. Curettage appears to be most efficacious (even for children) but is painful and requires anesthesia and a large time commitment over the course of several visits; it also has a risk of scarring. Relapse is common.
- **Imiquimod 5% (Aldara):** An immune response modifier; stimulates production of interferon-alfa and other proinflammatory cytokines, inducing a tissue reaction associated with viral clearance from the skin. Apply TIW for up to 16 weeks or QPM for 4 weeks. Clearing can take up to 3 months. Limited studies; painless.
- **Podophyllotoxin:** Can be administered by a health care provider and washed off after 1-4 hours. This treatment is caustic, may cause significant irritation, and has limited effectiveness. It is contraindicated for use during pregnancy. Patient-administered podophyllotoxin (Podofilox) may be a safer alternative to podophyllum. Adverse effects include burning, pain, inflammation, erosion, and itching.
- **Cantharidin 0.7%:** Can be applied by a health care provider. One study of 300 children found that lesions cleared after two visits. This treatment may cause allergic reactions, stinging, and blistering. Do not use cantharidin around the eyes.

- **Tretinoin (Retin-A) 0.1% cream:** Can be applied to lesions BID. Adverse effects include drying, peeling, irritation, and soreness.
- **Trichloroacetic acid:** Can be administered by a health care provider. Controlling the depth of acid penetration is difficult. Adverse effects include pain and irritation; mild scarring is common.
- **A combination of salicylic and lactic acid:** Response is highly variable and recurrence is common.
- **Laser therapy:** Safe, efficient, tolerable, and efficacious.
- **Cidofovir 1-3% topical cream:** Applied BID for 2 weeks, followed by a 30-day rest period and then two additional cycles. This treatment has been shown to be effective in several small studies and case reports, but it is expensive and difficult to compound. No systemic adverse effects are noted.
- **Silver nitrate paste:** May be used to burn each lesion individually.

Patient Education

- Molluscum infection is benign but may be distressing.
- Molluscum infection may be transmitted both sexually and nonsexually, through direct contact with lesions. Molluscum also can be transmitted indirectly by contact with infected objects.
- Latex condoms or barriers may not prevent transmission of genital molluscum.
- To prevent the spread of molluscum, instruct patients to take the following precautions:
 - Avoid close contact between their molluscum lesions and the skin, mouth, and genitals of other people.
 - Avoid picking at, squeezing, or puncturing the lesions, as a lesion's central plug is full of viral particles that can be spread easily by coming into contact with other parts of the body. In addition, lesions may become secondarily infected.
 - Wash hands frequently.
 - Keep fingernails short.
 - Avoid shaving in areas with lesions because shaving could result in lesions spreading to other areas.
 - Avoid sharing towels, bedclothes, clothing, shaving utensils, bathing equipment, or other objects that have been in contact with molluscum lesions.
 - Wash all contaminated items in very hot, but not scalding, water.
 - Cover lesions with clothing, if possible.

***Mycobacterium avium* Complex Disease**

Background

Mycobacterium avium complex (MAC) disease is an opportunistic infection caused by species of *Mycobacterium* that can produce severe illness in people with advanced AIDS but rarely affects others. The risk of disseminated MAC (DMAC) is directly related to the severity of immunosuppression. DMAC typically occurs in persons with CD4 counts of <50 cells/ μ L, and its frequency increases as the CD4 count declines. In the absence of antibiotic prophylaxis, DMAC occurs in up to 40% of AIDS patients with CD4 counts of <50 cells/ μ L. Antimicrobial therapy, especially if given in conjunction with antiretroviral therapy (ART) that achieves immune reconstitution, can be successful in treating MAC disease. Specific antimicrobial prophylaxis and effective ART also may be used to prevent MAC in patients with advanced AIDS (see chapter *Opportunistic Infection Prophylaxis*).

MAC organisms are common in the environment. They are found worldwide and have been isolated from soil, water, animals, birds, and foods. They usually enter the body through the respiratory or gastrointestinal tract and disseminate to cause multisystem infection, typically manifested by nonspecific symptoms and signs such as fever, sweats, weight loss, abdominal pain, fatigue, chronic diarrhea, and anemia and other cytopenias. MAC also can cause local disease such as central nervous system infection, lymphadenitis, soft-tissue or bone infections, and rarely, isolated pulmonary disease. Focal MAC disease is more common among patients on ART, whereas DMAC is the more common manifestation among those with low CD4 cell counts who are not on ART. Unlike *Mycobacterium tuberculosis*, *Mycobacterium avium* is not thought to be transmitted via person-to-person contact. In patients with subclinical or incompletely treated MAC who have recently started ART, an immune reconstitution inflammatory syndrome (IRIS) may occur with localized lymphadenitis or paradoxically worsening symptoms (see chapter *Immune Reconstitution Inflammatory Syndrome*).

S: Subjective

The patient complains of one or more of the following symptoms:

- Persistent or cyclic fever
- Night sweats
- Unintentional weight loss
- Anorexia
- Chronic diarrhea
- Weakness
- Fatigue
- Abdominal pain
- Lymph node enlargement

When taking the history, ask about the following:

- Any symptoms as described above, including duration and intensity; other symptoms of infection
- Whether the patient is taking MAC prophylaxis or ART

O: Objective

Perform a full physical examination with particular attention to the following:

- Vital signs (temperature, heart rate, blood pressure, respiratory rate)
- Weight (compare with previous measurements)

- General appearance (cachexia, wasting, signs of chronic illness, jaundice, pallor)
- Lymph nodes (lymphadenopathy)
- Abdomen (hepatosplenomegaly, tenderness)

Review previous laboratory values, particularly the CD4 count (usually <50 cells/ μ L).

A: Assessment

Rule out other infectious or neoplastic causes of constitutional symptoms, anemia, or organomegaly. A partial differential diagnosis would include the following:

- *M. tuberculosis* infection
- Cytomegalovirus infection
- Lymphoma
- Bartonellosis
- Disseminated fungal infection
- Pyogenic abscess
- Other septicemia

P: Plan

Diagnostic Evaluation

Definitive diagnosis requires identification of MAC in blood or other normally sterile body fluids or tissues (*M. avium* cultured from sputum, bronchial washing, or stool may represent colonization rather than infection). Send blood for acid-fast bacilli (AFB) culture (sensitivity of a single blood culture for MAC bacteremia is 91%, sensitivity increases to 98% if two samples [drawn at different times] are sent). Because MAC may take weeks to grow in culture, ancillary studies should be performed. The following are not specific, but may be helpful in reaching a presumptive diagnosis:

- AFB smear
- Complete blood count (CBC) for anemia, lymphopenia, and thrombocytopenia
- Serum alkaline phosphatase (often elevated in DMAC)

- Computed tomography (CT) scan of the chest and abdomen (intraabdominal and mediastinal lymphadenopathy or hepatosplenomegaly often are present)

If blood cultures are negative and MAC is suspected (or if results of blood cultures are pending), consider biopsy of the lymph nodes, bone marrow, liver, or bowel (via endoscopy) to detect DMAC by microscopic examination for AFB and culture. If the evidence suggests pulmonary MAC, consider bronchoscopy and bronchoalveolar lavage. Note that in MAC IRIS, MAC bacteremia usually is absent and a tissue-based diagnosis is required.

Perform additional studies as indicated to rule out other causes of the patient's symptoms, including bacterial blood cultures, sputum for *M. tuberculosis*, *Bartonella* studies, lymph node cytology for lymphoma, and stool cultures, as appropriate.

Treatment

Because antimicrobial resistance develops quickly with single-drug therapy, multidrug regimens must be administered for DMAC.

Preferred regimens:

- Clarithromycin 500 mg BID + ethambutol 15 mg/kg QD
- Azithromycin 500-600 mg QD + ethambutol 15 mg/kg QD (see below)

Clarithromycin is the preferred cornerstone of MAC therapy, as it has been studied more extensively and is associated with more rapid clearance of MAC bacteremia. If clarithromycin cannot be tolerated or if there is concern regarding drug interactions, azithromycin may be substituted for clarithromycin, as above. Clarithromycin dosages should not exceed 1 g per day, as high-dose clarithromycin has been associated with excess mortality.

Some experts recommend including a third agent for patients with more advanced HIV disease or higher MAC burden in blood cultures, and for those who are not receiving

effective ART. The addition of rifabutin (300 mg QD) has been associated with a mortality benefit in one study and with reduced emergence of mycobacterial resistance in two other trials; however, these studies were done before potent ART was available; the possible benefit of rifabutin in patients treated with effective ART has not been established. A fluoroquinolone (e.g., levofloxacin, moxifloxacin), amikacin, or streptomycin may be used instead of rifabutin as a third agent, or in addition to rifabutin as a fourth agent; however, studies have not confirmed the

clinical benefit of these medications.

Because immune reconstitution is essential for controlling MAC, all patients who are not already receiving ART should begin ART, if possible. Current guidelines recommend initiation of ART after 2 weeks of MAC treatment, for patients who are not already on ART. This strategy may decrease the risk IRIS and it serves to forestall interactions between DMAC and ARV drugs and the additive toxicities of those medications. Patients who are receiving suboptimal ART should be changed to suppressive regimens, if possible.

Potential ARV Interactions

Clarithromycin and rifabutin have a number of significant drug interactions, including interactions with some commonly prescribed ARVs. These interactions should be reviewed prior to initiation of MAC therapy. Dosage adjustments or alternative medications may be required. Azithromycin does not have significant interactions with ARVs.

Interactions of concern include the following:

Clarithromycin:

- **Atazanavir** may raise clarithromycin levels by 90%; some experts recommend using azithromycin in place of clarithromycin, or dosage reduction of clarithromycin by 50%.
- **Darunavir** increases clarithromycin levels; alternative agent (azithromycin) or dosage reduction of clarithromycin is recommended for patients with renal impairment.
- **Lopinavir/ritonavir and other protease inhibitors** may increase clarithromycin levels; alternative agent (azithromycin) or dosage reduction of clarithromycin is recommended for patients with renal impairment.
- **Efavirenz** may lower clarithromycin levels; avoid this combination if possible.
- **Etravirine** may lower clarithromycin levels, while clarithromycin may in turn increase etravirine levels. Avoid this combination, if possible.
- **Nevirapine** may decrease clarithromycin levels and increase levels of its active metabolite. Avoid this combination, if possible.
- **Elvitegravir/cobicistat** may increase clarithromycin levels. Dosage reduction of clarithromycin is required for patients with renal insufficiency.

Protease inhibitor-based ART (e.g., lopinavir or darunavir) or integrase inhibitor-based ART may be the preferred HIV treatment for patients on MAC therapy, because of limited drug interactions associated with those ARV classes.

Rifabutin has significant interactions with many drugs, including nonnucleoside reverse transcriptase inhibitors, protease inhibitors, and elvitegravir/cobicistat; therefore, dosage adjustments or alternative agents may be needed (for further information, see chapter *Mycobacterium tuberculosis*).

The patient should show clinical improvement within the first weeks of treatment. If there is not a response to treatment after 2-4 weeks, assess adherence, consider adding one or more drugs, and consider evaluation for other or additional causes of the patient's symptoms. Repeat a blood culture with antimicrobial sensitivities for patients whose clinical status has not improved after 4-8 weeks of treatment. Interpretation of MAC drug susceptibility testing should be undertaken in consultation with an infectious disease or HIV specialist, because laboratory evidence of drug resistance does not always correlate with clinical drug resistance.

If immune reconstitution inflammatory reactions are suspected, consider adding antiinflammatory medications, including corticosteroids if moderate to severe MAC IRIS symptoms do not improve with NSAIDs (see chapter *Immune Reconstitution Inflammatory Syndrome*).

Treatment of MAC generally is required for the remainder of the patient's life in the absence of immune reconstitution with effective ART. It may be reasonable to discontinue MAC therapy if patients complete at least 12 months of MAC treatment, have no further symptoms, and demonstrate immune restoration in response to ART (an increase in CD4 counts to >100 cells/ μ L for at least 6 months). If MAC treatment is discontinued, the patient must be monitored carefully for any decrease in CD4 cell count or recurrence of MAC symptoms. Treatment should be resumed if the CD4 count drops to <100 cells/ μ L or if symptoms recur.

Prevention

Primary prevention using azithromycin or clarithromycin should be initiated in persons with CD4 cell counts of <50 cells/ μ L. See chapter *Opportunistic Infection Prophylaxis*.

Patient Education

- Advise patients that antimycobacterial therapy alone will not eradicate MAC infection, but should decrease symptoms and improve quality of life. A response to treatment may take up to 4 weeks. If medications are discontinued, the disease almost always recurs, unless the CD4 count has increased to >50 - 100 cells/ μ L in response to ART.
- Patients must take all medicines exactly as prescribed. If doses are missed, or if the medication is stopped and restarted, MAC can develop resistance to the medications. If patients are having trouble taking the medications on schedule, they should contact their health care provider promptly.
- Advise patients that MAC IRIS is a common complication of effective ART and MAC therapy, and its occurrence in the course of treatment should be anticipated.
- Urge patients to contact the clinic immediately if they notice worsening of existing symptoms or the development of new symptoms.
- DMAC is an opportunistic infection of late-stage HIV and it is indicative of profound immunosuppression. Some patients may not respond to MAC treatment or to ART. Because this is a life-threatening disease, clinicians should discuss advance directives and durable power of attorney with patients. Referral to a social worker, mental health clinician, or chaplain experienced in such issues may facilitate the discussion.

Mycobacterium tuberculosis

Background

In HIV-infected individuals, tuberculosis (TB) causes more deaths worldwide than any other condition. A biologic synergy exists between HIV and TB such that HIV-induced immunosuppression increases susceptibility to active TB infection, whereas active TB infection increases HIV progression and risk of death. The populations infected by these two pathogens overlap in many respects, creating epidemiologic synergy. Poverty, crowded living conditions, and inadequate interventions to reduce transmission and treat latent TB infection (LTBI) combine to enhance the transmission of both organisms.

In the United States, more than 60% of TB cases occur in foreign-born individuals, with the majority of these cases attributed to reactivation of LTBI. In 2010, only 8% of active TB cases occurred in patients known to be infected with HIV, and TB is a relatively infrequent AIDS-defining illness. Nevertheless, TB remains important to HIV clinicians in the United States because it can be highly infectious and challenging to diagnose, and because improper treatment may lead to drug resistance both in the infected patient and in individuals to whom that patient transmits. Although other conditions increase the risk of TB disease (e.g., malnutrition, diabetes, end-stage renal disease, pulmonary silicosis, and iatrogenic immunosuppressive drugs [especially inhibitors of tumor necrosis factor]), HIV infection remains an important risk factor.

TB is an infection caused by *Mycobacterium tuberculosis* (MTB) complex. These organisms grow slowly and can be identified only with special staining techniques, a trait that led to the name “acid-fast bacteria.” This chapter focuses on disease caused by *M. tuberculosis*; other chapters describe diagnosis and management of latent MTB infection (see chapter *Latent Tuberculosis Infection*) and diagnosis and management of disease caused by *Mycobacterium avium* (see chapter *Mycobacterium avium Complex Disease*).

MTB most often causes a chronic pneumonia, but it can affect organs other than the lungs as well. The lung destruction caused by MTB may create cavities, similar to abscesses; these contain huge numbers of organisms. TB is transmitted almost always by persons with active pulmonary TB who release large numbers of organisms in their sputum. Patients with smear-positive sputum are the most infectious; however, transmission from patients with AFB smear-negative, culture-positive sputum has been well documented. Extrapulmonary tuberculosis generally is not considered contagious.

MTB organisms are inhaled and infect the lung. In most people, the initial lung infection is contained by an effective immune response. It usually is asymptomatic but leads to foci in the lung (and sometimes in other organs) of latent TB, which may reactivate and cause active TB disease years later. Shortly after the onset of infection with MTB, before its containment in the lung by the immune system, organisms can spread to other organs and establish latent infection in those areas as well. Reactivation in these other organs can lead to local disease (e.g., in the lymph nodes, meninges, bone, pericardium, peritoneum or intestine, and urogenital tract).

Persons with impaired immunity, such as persons with HIV-associated immunosuppression and very young children, are at high risk of developing progressive primary TB at the time of initial MTB infection. Primary progressive MTB usually causes pulmonary disease, but also can

cause meningitis or disseminated disease (blood, liver, spleen, lung, and other organs). Persons who have latent TB infection and then develop immunodeficiency are at high risk of developing reactivation disease. For example, compared with the <10% lifetime risk of developing active TB in immunologically normal persons, an HIV-infected person with latent TB has about a 10% chance each year of developing active disease. Even with immune reconstitution through antiretroviral therapy (ART) and a normalized CD4 cell count, HIV-infected patients remain at elevated risk of reactivation TB, compared with the background community risk of TB.

Classical pulmonary tuberculosis, with upper-lobe infiltrates and cavitary lesions, may occur in HIV-infected persons with relatively intact immunity. As the CD4 count decreases (particularly to <200 cells/ μ L), TB is more likely to manifest atypically in the chest (without cavitary disease) or with lower-lobe disease, adenopathy, pleural effusions, or interstitial or military infiltrates), and as extrapulmonary or multiorgan disease (particularly in lymph nodes, peritoneum, pericardium, and meninges). Granulomas may be seen in the tissues; in persons with advanced immunodeficiency, these may be poorly formed and non-caseating. Bone, joint, and urogenital TB are less-commonly associated with HIV-induced immunosuppression. Symptoms and signs in HIV-infected persons therefore can vary widely and can be difficult to distinguish from HIV-related opportunistic infections and malignancies.

Appropriate use of modern chemotherapy with rifampin-containing TB treatment applied to drug-susceptible MTB disease cures at least 95% of these patients, including those with HIV coinfection. However, drug resistance seriously reduces the cure rate. Drug resistance usually is caused by improper or erratic treatment. It is spreading rapidly and becoming more severe. Effective diagnosis and cure of drug-susceptible TB not only reduces the disease burden in the individual and reduces further transmission, it also is crucial to avoiding drug resistance.

MTB resistance to a single drug may extend or complicate treatment but usually does not prevent successful treatment of TB. Resistance to both isoniazid and rifampin, with or without resistance to other first-line drugs, is called **multidrug resistance (MDR)**, and it makes treatment especially difficult. **Extreme drug resistance (XDR)** occurs when, in addition to isoniazid and rifampin resistance, there is resistance to specific second-line drugs: a fluoroquinolone plus an injectable agent (kanamycin, amikacin, or capreomycin). Treatment of drug-resistant TB should be managed by experts or in consultation with experts. MDR TB is uncommon in the United States; it occurred in 1.3% of cases in 2010, and the great majority of these were foreign-born patients (82.6%). XDR is very rare in the United States, with only 4 cases reported in 2010.

Effective antiretroviral treatment (ART) is a critical component of the care of persons with TB, and ART should be initiated or optimized in all persons with active TB, regardless of their current CD4 cell count.

This chapter will discuss the evaluation and management of TB in the United States and other high-income settings. For management of TB in resource-limited settings, see the relevant World Health Organization guidelines and other resources.

S: Subjective

Persons with TB generally describe an illness lasting several weeks to months, associated with systemic features such as high fevers, night sweats, loss of appetite, and weight loss. These symptoms are nonspecific, but should raise the possibility of TB.

- Pulmonary TB presents with a chronic productive cough and sometimes with hemoptysis; shortness of breath occurs late in the disease course.
- TB adenitis presents with enlarged lymph nodes (usually asymmetric involvement in one region) that may suppurate and drain but usually are not painful, hot, or erythematous.
- TB meningitis presents with headache, gradual change in mental status, and at times with cranial nerve abnormalities such as double vision or decreased hearing.
- Disseminated TB may occur with systemic manifestations such as fever, sweats, and weight loss, with no localizing features.

Risk factors for TB infection include known prior contact with an active case, exposure in congregate settings (such as homeless shelters and prisons, but also in health care facilities), travel or residence in countries with high rates of endemic TB, and birth in a TB-endemic country (more than half of foreign-born individuals diagnosed with TB in the United States originated from one of the following five countries: Mexico, the Philippines, Vietnam, India, or China). In the United States, persons with active or past substance-use disorders and persons of color are more likely than others to have had exposure to TB. History of a prior positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) result provides evidence of previous TB exposure; however, up to 35% of patients with active TB will have a negative TST or IGRA result (see chapter *Latent Tuberculosis Infection*). Risks for active TB disease include any degree of HIV-associated immunosuppression, immunosuppression

associated with other diseases (e.g., leukemia, lymphoma) or caused by medical therapies (e.g., tumor necrosis factor-alpha blockers such as etanercept), and malnutrition.

O: Objective

- Measure vital signs, including oxygen saturation.
- Measure weight; compare with previous values.
- Perform thorough physical examination with particular attention to the lungs, heart, abdomen, lymph nodes, skin, and neurologic system.

Systemic signs of chronic disease and inflammation are common, including cough, fever, night sweats (which may occur without awareness of the high fever that precedes them), and weight loss.

In patients with pulmonary TB, the breath sounds may be normal or focally abnormal; tachypnea and hypoxia occur only with extensive lung damage.

Extrapulmonary TB may present with focal adenopathy without local signs of inflammation, but perhaps with a draining sinus.

TB meningitis presents as subacute or chronic meningitis, with neck stiffness and changes in mental status. Symptoms may include cranial nerve palsies owing to inflammation at the base of the brain or increased intracranial pressure.

Pericardial disease can cause the pain and friction rub of pericarditis or signs of pericardial tamponade.

Infiltration of the bone marrow can produce pancytopenia.

Disseminated TB may cause diffuse adenopathy, hepatic or splenic enlargement, and abnormal liver function, although hepatic failure is rarely attributable to TB alone.

Infection of the adrenal glands can cause adrenal insufficiency.

A: Assessment

Note: If pulmonary TB is suspected, the patient should wear a mask while in the medical facility and the care provider should wear an N95 respirator during the examination to reduce transmission risk.

The differential diagnosis of TB is extensive and depends in part on the degree of immunosuppression (as indicated by the CD4 cell count) of the individual. It includes a broad range of bacterial, mycobacterial, viral, and fungal infections in addition to noninfectious causes. A partial differential diagnosis of pulmonary TB includes the following:

- Bacterial pneumonia
- Pulmonary *Mycobacterium* pneumonia (nontuberculous)
- *Pneumocystis jiroveci* pneumonia (PCP)
- *Cryptococcus neoformans* pneumonia/pneumonitis
- Pulmonary Kaposi sarcoma
- *Toxoplasma* pneumonitis
- Disseminated histoplasmosis
- Disseminated coccidioidomycosis
- Cytomegalovirus pneumonia
- Bronchogenic carcinoma
- Non-Hodgkin lymphoma
- Influenza
- Pulmonary embolus
- Chronic obstructive pulmonary disease
- Reactive airway disease
- Congestive heart failure
- Lactic acidosis

P: Plan

Diagnostic Evaluation

Initial evaluation

Suspected TB should be evaluated aggressively.

- During the initial evaluation, check complete blood count (CBC) and differential, sputum gram stain, sputum acid-fast bacilli (AFB) stain, culture, and nucleic acid amplification (NAA) test (see below), blood cultures, and chest X-ray.
- For patients with lymphadenopathy, consider fine-needle aspiration biopsy for bacterial and AFB stains and culture, and cytologic evaluation.
- For patients with meningitis or central nervous system (CNS) abnormalities, perform lumbar puncture (LP) and cerebral spinal fluid (CSF) analysis including cell count, protein, glucose, AFB smear and culture, and bacterial and fungal cultures.
- Computed tomography (CT) is recommended for all patients with HIV prior to LP, particularly if focal neurologic abnormalities are present.
- Perform other diagnostic tests as suggested by the clinical presentation.

Imaging

Pulmonary TB can be associated with any chest X-ray appearance, including a normal X-ray image. However, the chest X-ray classically demonstrates upper-lobe infiltrates with or without cavities. Patients with HIV infection (especially advanced HIV and low CD4 cell counts) are more likely to have atypical chest X-ray presentations, including absence of cavities, presence of lower-lobe disease, hilar or mediastinal adenopathy, and pleural effusions.

In disseminated TB, the chest X-ray may show a miliary pattern with small nodules ("millet seeds") scattered throughout both lungs.

AFB testing

TB should be diagnosed by identification of the organism in stained sputum smears or stains of tissue and confirmed by culture or NAA test. All positive cultures should undergo drug susceptibility testing. Proof of the diagnosis is important because other opportunistic diseases can mimic TB, and mycobacterial infections other than TB (e.g., MAC) can occur; these require different treatment. TB drug susceptibility testing is necessary to ensure appropriate treatment, to reduce the risk of developing further TB drug resistance, and to decrease the risk of transmission of drug-resistant TB. Three specimens of expectorated sputum should be sent for acid-fast staining and mycobacterial culture. A presumptive diagnosis of pulmonary TB can be made if AFB are seen, but confirmation is

required. Sputum induction with nebulized saline (e.g., by respiratory therapists) can be used for patients who do not have spontaneous sputum production. (Sputum induction has been successful in children, but for young children who cannot produce sputum, gastric lavage on three successive mornings can be performed to obtain swallowed sputum for smear [although false-positive results can occur] and culture.)

Current U.S. guidelines for treatment of opportunistic infections recommend NAA testing on at least one respiratory specimen (regardless of smear status) from each patient with signs and symptoms of pulmonary TB. The algorithm in Table 1 is recommended by the U.S. Centers for Disease Control and Prevention (CDC) for interpretation of NAA test results.

Table 1. Nucleic Acid Amplification Testing and Interpretation Algorithm

1. If the NAA result is positive and the AFB smear result is positive, presume the patient has TB and begin anti-TB treatment while awaiting culture results. The positive predictive value of FDA-approved NAA tests for TB is >95% in AFB smear-positive cases.
2. If the NAA result is positive and the AFB smear result is negative, use clinical judgment in deciding whether to begin anti-TB treatment while awaiting culture results and determine whether additional diagnostic testing is needed. Consider testing an additional specimen using NAA to confirm the NAA result. A patient can be presumed to have TB, pending culture results, if two or more specimens are NAA positive.
3. If the NAA result is negative and the AFB smear result is positive, a test for inhibitors should be performed and an additional specimen should be tested with NAA. Sputum specimens (3-7%) might contain inhibitors that prevent or reduce amplification and cause false-negative NAA results.
 - a. If inhibitors are detected, the NAA test is of no diagnostic help for this specimen. Use clinical judgment to determine whether to begin anti-TB treatment while awaiting results of culture and additional diagnostic testing.
 - b. If inhibitors are not detected, use clinical judgment to determine whether to begin anti-TB treatment while awaiting culture results and determine whether additional diagnostic testing is needed. A patient can be presumed to have an infection with non-TB mycobacteria if a second specimen is smear positive and NAA negative and has no inhibitors detected.
4. If the NAA result is negative and the AFB smear result is negative, use clinical judgment to determine whether to begin anti-TB treatment while awaiting results of culture and additional diagnostic tests. Currently available NAA tests are not sufficiently sensitive (detecting 50-80% of AFB smear-negative, culture-positive pulmonary TB cases) to exclude the diagnosis of TB in AFB smear-negative patients suspected of having TB.

Sensitivity of the NAA tests in smear-positive specimens is high but decreases to 50-80% in smear-negative, culture-positive specimens. The rapid identification of MTB facilitates appropriate respiratory infection control precautions, contact tracing, and immediate treatment of MTB. NAA tests also are useful in making a presumptive diagnosis in smear-negative patients who are suspected to have active pulmonary TB, pending culture results. However, these tests can yield false-positive results, particularly with persons in whom pulmonary TB is unlikely. Also, false negatives can occur in both smear-positive and smear-negative patients. NAA testing is not available in all laboratories and in some it is restricted to AFB smear-positive specimens.

The Xpert MTB/RIF is a rapid NAA test that was recently reviewed by the FDA and allowed to be marketed in the United States. This assay identifies TB and at the same time identifies rifampicin (RIF) resistance from a direct sputum sample. Data from high-prevalence TB settings show a sensitivity of >98% for TB in smear-positive specimens. Sensitivity in smear-negative specimens is 70% with a single test, and up to 90% with three tests, with a specificity of 99%. Other NAA tests can be used to rapidly identify clinically significant non-TB mycobacteria such as MAC and *Mycobacterium kansasii*. If a non-TB mycobacteria is diagnosed, respiratory precautions can be discontinued, and treatment for the specific or suspected organism can be started.

In patients with suspected pulmonary TB, negative sputum microscopy or NAA results do not rule out TB; and consideration should be given to starting empiric TB treatment while further evaluation is undertaken.

A diagnosis of extrapulmonary TB generally requires an examination of infected tissue or body fluid by microscopy and culture. NAA tests are approved for testing of sputum

samples, but have been used on tissue and body fluids (such as CSF); specimens that are fresh or frozen generally are preferable to specimens preserved in formalin or a similar chemical. Specimens of organs with suspected TB can be obtained by peripheral lymph node aspiration, CT-guided or other guided aspiration and biopsy, liver biopsy, bone marrow biopsy, or thoracoscopy- or laparoscopy-guided biopsies of pleura or peritoneum. In some cases, surgery is required to obtain appropriate specimens. Blood cultures for mycobacteria (using appropriate mycobacterial media rather than standard blood culture media) may be positive in disseminated TB, particularly with advanced HIV disease; the technique is the same as in culturing blood for MAC organisms. Urine culture is used to diagnose renal TB, although this condition is rare among HIV-infected persons.

Initial growth of MTB on culture may occur within 3-8 weeks. A nucleic acid probe can confirm a positive culture as MTB within few days of culture growth; otherwise, speciation may take several weeks. Susceptibility testing generally takes 3-4 weeks after the initial culture growth, depending on what laboratory procedures are used. Rapid tests for diagnosis of drug resistance allow early identification of resistance and optimization of treatment. The Xpert MTB/RIF assay is available in the United States, and others (including line probe assays, nitrate reductase assay, and phage-based assays) are available in other countries. Some health departments have in-house assays for rifampin resistance. NAA tests for TB drug resistance are efficient at screening for resistance against drugs for which a single mutation (e.g., rifampin) or a few mutations (e.g., isoniazid) are responsible. Rapid assays to detect mutations that confer resistance to other first- and second-line drugs are in development.

Note that a positive TST or IGRA result confirms TB infection but does not prove active disease (see chapter *Latent Tuberculosis*).

Similarly, a negative result may occur in up to 35% of HIV-infected persons with active TB and does not rule out TB disease. When a specific microbiologic diagnosis cannot be made or may be delayed (as with TB meningitis testing, for which CSF culture results may take weeks to obtain or may be negative), a positive TST or IGRA result can help support the diagnosis and implementation of therapy; however, a negative result on these tests does not rule out active TB.

Respiratory Precautions

Respiratory infection control precautions should be implemented for HIV-infected patients with an undiagnosed chronic cough or undiagnosed inflammatory infiltrate on chest X-ray. Individual institutions have specific guidelines that should be followed; patients usually are housed in single negative-pressure rooms and persons entering the rooms are required to wear protective respirators. Patients seen in the outpatient setting should wear a mask while in the medical facility, and providers should wear an N95 respirator when evaluating the patient. If three sputum smears yield negative results on AFB staining, or if a single deep specimen (bronchial lavage or tracheal aspirate) is smear negative, infectious TB is unlikely and respiratory precautions can be discontinued. Patients who are highly suspect for MTB and lack an alternative diagnosis may be kept on precautions and empiric treatment may be started, as transmission of TB from AFB smear-negative, culture-positive TB patients is well documented. Persons who have responded to treatment for an alternative diagnosis (e.g., bacterial pneumonia), and those who cannot produce the requisite three sputum samples, may be released from the TB precautions.

The impact of TB transmission is greater in a health care setting, where immunosuppressed persons may be exposed, than at home, where exposure has occurred prior to the TB evaluation. Of course, children younger than age 5 and immunosuppressed persons in the home are at increased risk.

Treatment

Treatment for TB should be instituted promptly when TB is considered likely and the proper specimens to prove the diagnosis have been obtained. It is ideal to have a positive smear result (and confirmation by NAA testing) prior to initiating treatment, but empiric treatment should be started while the initial specimens are collected from patients in whom the suspicion of TB is high, in severely ill persons, or in circumstances in which positive smear results are unlikely (e.g., suspected TB meningitis with AFB smear-negative CSF).

Randomized trials have demonstrated that ART decreases mortality in HIV-infected persons with active TB regardless of initial CD4 cell count; thus, effective ART should be initiated or optimized in everyone with TB/HIV coinfection; see “Coordinating with antiretroviral therapy,” below.

Adherence is the most important treatment issue once the decision to treat is made and an appropriate regimen is selected. *It is the responsibility of the treating clinician to ensure that the patient completes a full course of therapy.* Therefore, it is strongly recommended that patients be referred to public health departments for TB treatment. Health departments usually can provide free TB treatment and have specific resources and systems to promote adherence. It is recommended that all patients receive directly observed therapy (DOT), an approach by which the taking of every dose of anti-TB medication is observed and documented. Clinical trials have documented that DOT with enhancements to maximize adherence not only improves the rate of completion of therapy but also reduces mortality among HIV-infected TB patients. If a health department manages the TB treatment, the HIV clinician must coordinate with the health department for the following reasons: 1) to coordinate TB and HIV treatment regimens; 2) to avoid or adjust for drug interactions; 3)

to assist the health department in avoiding diagnostic or treatment confusion in the event of immune reconstitution inflammatory syndrome (IRIS) or incident opportunistic diseases; and 4) to maximize adherence with the TB medications, ART, opportunistic infection treatment or prophylaxis, and any other medications.

Treatment consists of two phases: intensive and continuation. Several intermittent therapy regimens have been designed to simplify DOT; however, use of TIW and BIW regimens during the intensive phase of treatment have led to higher rates of treatment failure and resistance, as have weekly or BIW continuation

phase regimens. **Thus, daily (or 5-7 days per week) dosing by DOT is recommended during the intensive phase of treatment,** and 5-7 days per week or TIW dosing is recommended during the continuation phase.

Preferred therapy (drug-susceptible pulmonary TB)

- **Intensive Phase:** Isoniazid + rifampin (or rifabutin) + pyrazinamide + ethambutol QD (5-7 days per week) for 8 weeks, by DOT
- **Continuation Phase:** isoniazid + rifampin or rifabutin 5-7 days per week or TIW

Table 2. Recommended Dosages of First-Line Antituberculosis Drugs for Adults

Drug	Daily	3 Times Weekly
Isoniazid	5 mg/kg (usual dose 300 mg)	15 mg/kg (usual dose 900 mg)
Rifampin[†]	10 mg/kg (usual dose 600 mg)	10 mg/kg (usual dose 600 mg)
Rifabutin*		
without HIV protease inhibitors, efavirenz, rilpivirine, or elvitegravir/cobicistat	5 mg/kg (usual dose 300 mg)	5 mg/kg (usual dose 300 mg)
with HIV protease inhibitors	150 mg	300 mg
with efavirenz	450-600 mg	450-600 mg
with elvitegravir/cobicistat*	150 mg	150 mg
Pyrazinamide		
40-55 kg body weight	1,000 mg (18.2-25.0 mg/kg)	1,500 mg (27.3-37.5 mg/kg)
56-75 kg body weight	1,500 mg (20.0-26.8 mg/kg)	2,500 mg (33.3-44.6 mg/kg)
76-90 kg body weight	2,000 mg (22.2-26.3 mg/kg)	3,000 mg (33.3-39.5 mg/kg)
>90 kg body weight	2,000 mg [#]	3,000 mg [#]
Ethambutol		
40-55 kg body weight	800 mg (14.5-20.0 mg/kg)	1,200 mg (21.8-30.0 mg/kg)
56-75 kg body weight	1,200 mg (16.0-21.4 mg/kg)	2,000 mg (26.7-35.7 mg/kg)
76-90 kg body weight	1,600 mg (17.8-21.1 mg/kg)	2,400 mg (26.7-31.6 mg/kg)
>90 kg body weight	1,600 mg [#]	2,400 mg [#]

[†] Rifampin is not recommended for patients receiving HIV protease inhibitors, efavirenz, nevirapine, rilpivirine, or elvitegravir/cobicistat. Dolutegravir, raltegravir, and maraviroc require dosage adjustment.

* Avoid coadministration of rifabutin with elvitegravir/cobicistat, if possible. If used together, consider therapeutic drug monitoring and dosage adjustment as indicated. Do not coadminister with rilpivirine.

[#] For patients weighing >90 kg, monitor for therapeutic response can consider therapeutic drug monitoring.

Four anti-TB drugs are administered for the first 2 months, then two drugs are administered for an additional 4 months (if the organism is susceptible to standard medications). The initial phase of TB treatment usually consists of isoniazid, rifampin or rifabutin (see below), pyrazinamide, and ethambutol; the continuation phase typically is simplified to isoniazid and rifampin. Pyridoxine (vitamin B6) at a dosage of 10-50 mg QD usually is included to minimize the risk of isoniazid-induced peripheral neuropathy. If drug resistance or MDR is suspected, more drugs can be used initially, and treatment should be directed by experts. Resistance may be suspected among persons exposed to TB in countries with high rates of endemic resistance, those for whom previous treatment has failed, those who have been on and off treatment erratically, those who may have had a specific exposure to drug-resistant TB, and those who have been diagnosed during an outbreak. If drug susceptibility testing shows sensitivity to isoniazid and rifampin, ethambutol can be discontinued during the intensive phase.

In certain circumstances, treatment duration is extended. In cavitary TB or TB in an HIV-infected person that remains sputum culture positive after 2 months of treatment, the two-drug continuation phase should be extended to 7 months for a total treatment course of 9 months. For extrapulmonary TB in HIV-infected persons, a 6- to 9-month course of treatment is recommended. Exceptions include meningeal TB, which is treated for 9-12 months. If cultures obtained prior to treatment demonstrate drug resistance, the regimen and the duration of therapy may need to be changed.

For TB meningitis or pericarditis, a course of corticosteroids may be given in addition to specific anti-TB therapy: dexamethasone 0.3-0.4 mg/kg/day for 2-4 weeks then tapered over

the course of 8-10 weeks or prednisone 1 mg/kg/day for 3 weeks followed by a taper over the course of 3-5 weeks. For adrenal insufficiency, replacement corticosteroids should be given.

Considerations During pregnancy

Pyrazinamide has not been formally proven safe for use during pregnancy; however, it is used during pregnancy in many countries and there have been no reports of problems. Some health departments in the United States avoid the use of pyrazinamide for pregnant women and extend the continuation phase to 7 months, whereas others prescribe the standard regimens shown in Table 2 during pregnancy. Streptomycin and certain second-line drugs should be avoided during pregnancy. HIV-infected women in the United States are instructed not to breast-feed, so there usually are no issues regarding TB treatment of HIV-infected women during breast-feeding. ART should be started as early as possible; consult with an expert.

Coordinating with Antiretroviral Therapy

ART and TB treatment must be coordinated for both to be successful. ART is strongly recommended for all adults and adolescents with active TB, and both randomized and nonrandomized trials have demonstrated reduction in mortality when ART is combined with anti-TB chemotherapy.

The optimal timing of ART initiation in relation to TB treatment has been established with several randomized controlled trials. Adults and adolescents with active TB and CD4 counts of <50 cells/ μ L should start ART within 2 weeks of starting TB treatment. All patients with CD4 counts of \geq 50 cells/ μ L should start ART within 8-12 weeks of starting TB therapy, but those who have CD4 counts of 50-200 cells/ μ L and severe disease should start within 2-4 weeks, if possible. Further, current HHS ARV guidelines recommend consideration of early ART (within 2-4 weeks)

for patients with CD4 counts of >200 cells/ μ L and severe disease. In all cases, TB treatment should be started immediately.

Timing of ART initiation in CNS TB infection is not clear. In one randomized trial, there was not a mortality benefit to starting ART at 2 weeks after TB treatment initiation compared with starting after 2 months of TB treatment, and more severe adverse events occurred in the earlier ART arm. Given the capacity for close monitoring that exists in the United States, many experts recommend initiating ART as with non-CNS TB.

Although paradoxical immune response (i.e., IRIS, see below) appears to be more common in patients who start ART earlier in the course of TB treatment, IRIS generally is not fatal.

Drug-drug interactions

Drug interactions between TB medications and ARVs may require dosage adjustments or modifications in treatment (see Table 3). Rifampin is a potent inducer of cytochrome P450 enzymes and has many clinically important drug interactions. It reduces the blood levels of nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors, and the CCR5 antagonist maraviroc, but does not affect nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) or the fusion inhibitor enfuvirtide. Triple-nucleoside regimens can be administered safely during rifampin treatment but are less potent than first-line ARV combinations and generally are not recommended. Current guidelines recommend the use of efavirenz plus a two-drug NRTI backbone if cotreatment with rifampin is planned (see Table 3). Efavirenz blood levels may be reduced 25% by concomitant rifampin, but the majority of available clinical data suggest that the standard efavirenz dosage of 600 mg/day is appropriate for rifampin coadministration, particularly in African-American and Asian populations. Limited clinical data support

the use of nevirapine at standard dosages in combination with rifampin. This is not a favored approach because nevirapine levels are reduced up to 50% when combined with rifampin. In one study, 20% of patients on ARV and TB treatment with rifampin had trough nevirapine levels that were below target, although they achieved the same rates of HIV RNA suppression as did patients on efavirenz. Plasma levels of the integrase inhibitors raltegravir and dolutegravir also are reduced when they are given with rifampin but the interaction can be overcome by increasing the dosage of the integrase inhibitor; few clinical data are available on the use of integrase inhibitors with rifampin.

To avoid rifampin-ARV interactions, rifabutin typically is used in place of rifampin. Rifabutin has fewer marked effects on the pharmacokinetics of other drugs, although its own blood concentrations can be affected by certain ARVs. Dosing recommendations for rifabutin with ARVs are found in Table 3. Acquired rifamycin resistance has been reported with coadministration of rifabutin with protease inhibitors, leading to the recommendation that the rifabutin dosage be at least 150 mg daily when given with ritonavir-boosted PIs and that monitoring of serum rifabutin levels be considered. Rifabutin is expensive; some public health systems do not provide rifabutin as part of TB treatment and it often is not available in resource-limited countries. The FDA characterizes rifabutin in pregnancy category B: it has been safe in animal studies of pregnancy but has not been proven safe for humans. For pregnant women who require both TB and ARV therapy, the use of rifabutin rather than rifampin allows the use of non-efavirenz-based ARV regimens.

Persons who are already on ART when TB treatment is begun must have their ARV regimens reassessed; the appropriate dosages of rifampin or rifabutin must be chosen or the ARV regimen must be modified, at least until completion of TB treatment (see Table 3).

Table 3. Interactions Between Antiretroviral Medications and Rifampin or Rifabutin: Contraindicated Combinations and Dosage Adjustments*

Antiretroviral Agent	Rifampin	Rifabutin* (Preferred in combination with PIs)
Nonnucleoside Reverse Transcriptase Inhibitors		
Efavirenz**	↓ efavirenz AUC; use standard efavirenz dosage 600 mg QD with monitoring for virologic efficacy (consider 800 mg QD if weight >60 kg).	Use standard efavirenz dosage. Increase rifabutin to 450-600 mg daily.
Etravirine	↓ etravirine levels expected; do not coadminister.	Etravirine without ritonavir-boosted PI: rifabutin 300 mg QD. Etravirine with a boosted PI: avoid, or consider therapeutic drug monitoring or rifabutin.
Nevirapine	↓ nevirapine levels; avoid if possible. If used, initiate nevirapine at 200 mg BID (no lead-in dosage); do not use nevirapine extended-release formulation.	↓ nevirapine and ↑ rifabutin levels. No dosage adjustment recommended; use cautiously.
Rilpivirine	↓ rilpivirine levels; do not coadminister.	↓ rilpivirine levels; do not coadminister.
Protease Inhibitors		
All protease inhibitors	↓ protease inhibitor levels; do not coadminister.	↑ rifabutin levels; adjust rifabutin dosage to 150 mg QD. Monitor for anti-TB efficacy, consider therapeutic drug monitoring.
Integrase Inhibitors		
Dolutegravir	↓ dolutegravir levels; increase dolutegravir to 50 mg BID for integrase-naïve patients (avoid if integrase resistance).	No dosage adjustment.
Elvitegravir/cobicistat	↓ elvitegravir and cobicistat levels expected; do not coadminister	↓ elvitegravir and ↑ rifabutin levels; do not coadminister.
Raltegravir	Increase raltegravir dosage to 800 mg BID; monitor for virologic response.	No dosage adjustment.
CCR5 Receptor Antagonists		
Maraviroc	↓ maraviroc levels; coadministration not recommended. If maraviroc must be used: Without a strong CYP 3A4 inhibitor: maraviroc 600 mg BID. With a strong CYP 3A4 inhibitor: maraviroc 300 mg BID.	Possible ↓ maraviroc levels. Without a strong CYP 3A4 inhibitor: maraviroc 300 mg BID. With a strong CYP 3A4 inhibitor: maraviroc 150 mg BID.
Fusion Inhibitors		
Enfuvirtide	No dosage adjustment.	No dosage adjustment.

Note: Rifapentine should not be coadministered with NNRTIs, PIs, or maraviroc.

* If available, rifabutin may be substituted for rifampin when TB treatment and ART are combined.

** Avoid use of efavirenz during early pregnancy and with women who may become pregnant while on therapy. Both rifampin and rifabutin significantly reduce estrogen and progestin levels for women on hormonal contraceptives; efavirenz raises estrogen levels moderately. Two forms of birth control, including one barrier method and either a mid- to high-dose hormonal contraceptive or an intrauterine device, are recommended most often.

Monitoring for efficacy

Ideally, every dose of anti-TB therapy is observed and documented by a health care agent or responsible individual, particularly during the intensive phase. Patients' adherence should be evaluated by a health care team member at least weekly during the initial phase of treatment and at least weekly or monthly during the continuation phase. If gaps in medication use occur, the cause must be evaluated and a plan to improve adherence must be implemented.

In treatment of pulmonary TB, monthly sputum specimens should be obtained for smear and culture until two sequential specimens are sterile on culture. Patients with extrapulmonary and disseminated TB usually are monitored clinically and with imaging studies. Biopsies are not repeated but other specimens (CSF and other body fluids) may be obtained for repeat AFB smear and culture. Monitoring of patients with extrapulmonary and disseminated TB should be done in consultation with an expert.

Immune reconstitution inflammatory syndrome

Patients on treatment for active TB who begin ART may experience a paradoxical increase in signs and symptoms of TB (fever, dyspnea, increased cough, enlarging lymph nodes, worsening chest X-ray findings, increased inflammation at other involved sites, or enlargement of CNS tuberculomas). These often are attributable to an enhanced immune response against remaining MTB organisms that occurs because of immunologic improvement from ART. IRIS may occur at any point from within 2 weeks up to several months after ART is initiated. TB treatment failure (potentially owing to an inappropriate treatment regimen, inadequate adherence, or drug resistance) must be ruled out, and the possibility of drug toxicity should be considered. In addition, new presentation

of opportunistic infection or malignancies should be considered. Paradoxical IRIS is a clinical diagnosis, and it can be made only after alternative diagnoses are excluded. If IRIS is diagnosed, TB and HIV treatment should be continued and symptoms can be managed with nonsteroidal antiinflammatory drugs or, in severe cases, with corticosteroids. Many experts recommend the use of corticosteroids particularly in the case of TB IRIS involving the CNS (see chapter *Immune Reconstitution Inflammatory Syndrome*).

Adverse effects of anti-TB medications

Anti-TB medications may have significant adverse effects. The most important adverse reactions reported for the commonly used anti-TB medications are listed in Table 4. The most frequent toxicities of first-line TB medications include hepatic enzyme elevations. Before initiating TB treatment, conduct a complete blood count with platelet count, serum creatinine count, liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, alkaline phosphatase), and hepatitis B and C serology. Newly diagnosed TB patients with unknown HIV status should be tested for HIV infection.

Patients should be monitored monthly with a symptom review to assess possible toxicity, and laboratory tests should be performed if symptoms suggest adverse effects. For patients with liver disease, it may be prudent to perform routine laboratory monitoring after 1 month on treatment and every 3 months thereafter. Persons with symptoms and aminotransferase elevations ≥ 3 times the upper limit of normal, and asymptomatic persons with aminotransferase elevations ≥ 5 times the upper limit of normal, should have therapy interrupted and should be managed thereafter in consultation with an expert.

Patients should be monitored for isoniazid-induced peripheral neuropathy; this adverse

effect is rare if pyridoxine is administered with isoniazid, as recommended. Testing of visual acuity and red-green color vision is recommended at the start of therapy with ethambutol. Persons on standard ethambutol dosages with normal baseline examinations

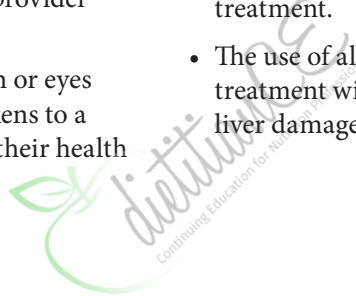
should be asked monthly about visual disturbances. Patients on higher ethambutol dosages and those who have been on ethambutol for more than 2 months should have periodic eye examinations for acuity and color discrimination.

Table 4. Adverse Events Associated with Common Anti-TB Medications

Medication	Common Toxicity	Rare Toxicity
First-Line Agents		
Isoniazid	Transient transaminase elevation, hepatitis, positive antinuclear antibody (ANA)	Peripheral neurotoxicity, lupus-like syndrome, CNS effects, hypersensitivity, rash, monoamine poisoning
Rifampin	Transient bilirubin elevation, transaminase elevations, anorexia, nausea, vomiting, hepatitis, red-orange discoloration of urine and tears	Acute renal failure, shock, thrombocytopenia, rash, "flu" syndrome from intermittent doses, pseudomembranous colitis, pseudoadrenal crisis, osteomalacia, hemolytic anemia
Rifabutin	Elevated liver function tests, nausea, red-orange discoloration of urine and tears	Cytopenias, uveitis, rash
Ethambutol	Optic neuritis	Skin rash, joint pains, peripheral neuropathy
Pyrazinamide	Joint pains, gout, hepatitis	Gastrointestinal symptoms, skin rash, sideroblastic anemia
Streptomycin	Auditory and vestibular nerve damage, renal injury	Rash
Second-Line Agents		
Moxifloxacin	Nausea, diarrhea, dizziness	Tendon rupture, hepatotoxicity, renal damage, prolonged QT interval, skin reactions
Amikacin/ Kanamycin	Auditory, vestibular, renal injury	

Patient Education

- All patients with TB-positive sputum or bronchoscopy specimens can infect others with TB. All close contacts, especially children, should be screened for TB as soon as possible and given medication to prevent (or treat) active disease.
- The health department will be notified of each TB case and will provide the required follow-up care.
- Patients must take all medicines exactly as prescribed. If doses are missed, or if the medication is stopped and restarted, the TB bacteria can develop resistance to even the best medications and become even more dangerous. If patients are having trouble taking the medication on schedule, they should contact their health care provider immediately.
- If patients become ill, if their skin or eyes turn yellow, or if their urine darkens to a “cola” color, they should contact their health care provider immediately.
- Patients must keep all follow-up appointments. Blood tests will be done regularly to ensure that the liver is working well, and patients will be checked for medication adverse effects. They should show their health care provider all medications, vitamins, and supplements they are taking so that the provider can check for drug interactions.
- Rifampin and rifabutin will make urine, sweat, and tears turn orange; this is not harmful. They will cause staining of plastic contact lens; patients should avoid wearing contact lenses if they are taking rifamycins.
- Rifampin and rifabutin may cause birth control pills to become ineffective. An alternative method of contraception should be used when the patient is undergoing treatment.
- The use of alcohol should be avoided during treatment with TB drugs to avoid the risk of liver damage.



Pelvic Inflammatory Disease

Background

Pelvic inflammatory disease (PID) is the syndrome resulting from the ascent of microorganisms from the vagina and cervix to the uterine endometrium, fallopian tubes, ovaries, or contiguous abdominal structures. Many episodes of PID go unrecognized, because of lack of symptoms or mild, nonspecific symptoms (e.g., dyspareunia, abnormal bleeding, and vaginal discharge). Infecting organisms may include *Neisseria gonorrhoeae* (GC) and *Chlamydia trachomatis* (CT), which are sexually transmitted, as well as anaerobic bacteria (*Gardnerella vaginalis* or *Haemophilus influenzae*), gram-negative rods (*Escherichia coli*), *Streptococcus agalactiae*, gastrointestinal flora, and mycoplasmas (*Mycoplasma hominis*). It is thought that PID generally is caused by sexually transmitted diseases (STDs) and that additional organisms become involved after infection spreads and protective immunological barriers are disrupted.

Between 20% and 40% of women with cervical chlamydial infection and 10-20% of women with gonococcal infection eventually develop PID, but accurate estimates of the incidence of PID and infertility resulting from GC and CT are difficult to obtain. Hospitalizations for PID declined steadily throughout the 1980s and 1990s but remained relatively constant between 2000 and 2006, at approximately 80,000 annually.

PID is co-epidemic with HIV among some urban populations of reproductive age. Data on PID outcomes among HIV-infected women are limited. Many studies have documented no difference in length or severity of lower abdominal pain, vaginal discharge, fever, abnormal vaginal bleeding, or low back pain between HIV-infected and HIV-uninfected women with PID. However, there is a higher rate of tubo-ovarian abscesses and severe salpingitis and pyosalpinx among HIV-infected women.

Clinical presentation may include salpingitis, endometritis, tubal and ovarian abscess, and pelvic peritonitis, although PID may present with subtle or mild symptoms even in HIV-infected women. Long-term complications of PID may include infertility, ectopic pregnancy, pelvic adhesions, and chronic pain. After a single episode of PID, a woman's risk of ectopic pregnancy increases sevenfold. Approximately 13% of women are infertile after a single episode of PID, 25-35% after two episodes, and 50-75% after three or more episodes.

Diagnosis of PID usually is based on clinical findings, and providers should maintain a low threshold for diagnosing and promptly treating this disease, as it can wreak havoc on a woman's reproductive health. All women who are diagnosed with PID should be tested for GC and CT.

S: Subjective

The patient may complain of mild-to-moderate lower abdominal pain and tenderness, pain with intercourse, vaginal discharge, fever, chills, heavy menstrual bleeding, or other abnormal vaginal bleeding.

Inquire about the following during the history:

- Symptoms listed above, and duration
- Sexual history including new sex partner(s)

and episodes of unprotected sex

- Last menstrual period
- Previous diagnosis of gonorrhea or chlamydia
- Previous abdominal or gynecologic surgery
- History of recent intrauterine device (IUD) placement (the risk of PID associated with IUD use is confined primarily to the first 3 weeks after insertion)

O: Objective

Check vital signs with special attention to temperature (may be elevated or normal).

Perform a focused physical examination. Check abdomen (bowel sounds, distention, rebound, guarding, masses, suprapubic and costovertebral angle [CVA] tenderness); perform complete pelvic examination looking for abnormal bleeding or discharge; uterine, adnexal, or cervical motion tenderness; pelvic masses or adnexal enlargement.

A: Assessment

A partial differential diagnosis includes the following:

- Pregnancy, uterine or ectopic
- Ruptured or hemorrhagic ovarian cyst
- Dysmenorrhea
- Appendicitis
- Pyelonephritis
- Diverticulitis
- Irritable bowel syndrome
- Cystitis
- Uterine fibroids/leiomyomas
- Ovarian torsion
- Mittelschmerz
- Kidney stones
- Pyelonephritis

P: Plan

Diagnostic Evaluation

A diagnosis of PID usually is based on clinical findings; however, the following can support a diagnosis and help rule out other causes of abdominal pain:

- Pregnancy test
- Nucleic acid amplification tests (NAAT) or culture for GC and CT
- Microscopic examination of saline preparation of vaginal secretions

Often, diagnosis must be made and treatment initiated on the basis of clinical criteria. Current guidelines identify “minimal criteria” found on pelvic examination in patients with PID:

- Cervical motion tenderness, or
- Uterine tenderness, or
- Adnexal tenderness

The following signs support a diagnosis of PID:

- Oral temperature $>101^{\circ}\text{F}$ ($>38.3^{\circ}\text{C}$)
- Abnormal cervical or vaginal mucopurulent discharge
- Presence of abundant numbers of white blood cells on saline microscopy of vaginal secretions (this also can detect concomitant infections such as bacterial vaginosis and trichomoniasis)
- Elevated erythrocyte sedimentation rate (ESR)
- Elevated C-reactive protein (CRP)
- Laboratory documentation of cervical infection with GC or CT (the absence of infection from the lower genital tract, where samples are usually obtained, does not exclude PID and should not influence the decision to treat)

Definitive diagnosis may be made on the basis of:

- Endometrial biopsy with histopathologic evidence of endometritis
- Transvaginal sonogram or other imaging showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex
- Laparoscopic abnormalities consistent with PID

Treatment

Because clinical diagnostic criteria for PID are not always conclusive, presumptive diagnosis and early empiric treatment is common. The positive predictive value of a clinical diagnosis is 65-90%.

Empiric therapy for PID should be started in women who have one or more of the minimal criteria, plus pelvic or lower abdominal pain and risk factors for PID (sexually active young women, women at risk of STDs), unless another cause for the symptoms is identified.

Treatment considerations

Antimicrobial regimens must be broadly effective against likely pathogens (see below). HIV-infected women appear to respond as well to standard antibiotic regimens as do HIV-uninfected women. It is not known whether HIV-infected women with advanced immunosuppression should be treated more aggressively; decisions about whether to use oral or parenteral therapy must be individualized.

In the United States and elsewhere GC commonly is resistant to fluoroquinolone; thus, this class of antibiotics is no longer recommended for treatment of PID.

No evidence suggests that IUDs should be removed in women diagnosed with PID. However, caution should be used if the IUD remains in place, and close clinical follow-up is recommended.

The goals of treatment include the following:

- Alleviate the pain and systemic malaise associated with infection
- Achieve microbiological cure
- Prevent development of permanent tubal damage with associated problems, such as chronic pelvic pain, ectopic pregnancy, and infertility
- Prevent the transmission of infection to others

Indications for hospitalization of patients with PID include the following:

- Unsure diagnosis; surgical emergency cannot be excluded
- Pregnancy
- Patient does not respond clinically (within 72 hours) to oral antimicrobial therapy
- Tubo-ovarian abscess
- Severe illness with nausea and vomiting or high fever
- Inability to follow or tolerate outpatient regimen

Pregnancy

If the patient is pregnant, aggressive treatment is essential to prevent preterm delivery, fetal loss, and maternal morbidity. Some medications should be avoided to reduce the risk of fetal toxicity; these include doxycycline and gentamicin. Hospitalization for parenteral antibiotic therapy is recommended.

Antibiotic Regimens

Recommended Oral/Outpatient Regimens

- Ceftriaxone 250 mg IM in a single dose + doxycycline 100 mg PO BID for 14 days, with or without metronidazole 500 mg PO BID for 14 days
- Cefoxitin 2 g IM in a single dose and probenecid 1 g PO concurrently in a single dose + doxycycline 100 mg PO BID for 14 days, with or without metronidazole 500 mg PO BID for 14 days
- Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) + doxycycline 100 mg PO BID for 14 days, with or without metronidazole 500 mg PO BID for 14 days

Alternative Oral Regimens

If parenteral cephalosporin therapy is not feasible, consult with an expert. Limited evidence supports the use of amoxicillin/clavulanic acid with doxycycline, and azithromycin with or without metronidazole or ceftriaxone. Because of the prevalence of fluoroquinolone-resistant GC, use of fluoroquinolones is no longer recommended but may be considered, with or without metronidazole, if the community prevalence is low, the patient's risk of gonorrhea is low, and follow-up can be assured if the GC test result is positive. For more information, see the *CDC Sexually Transmitted Diseases Treatment Guidelines* (see "References," below).

Recommended Parenteral Regimens

- Cefotetan 2 g IV Q12H + doxycycline 100 mg PO BID

- Cefoxitin 2 g IV Q6H + doxycycline 100 mg PO BID
- Clindamycin 900 mg IV Q8H + gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) Q8H; single daily dosing (3-5 mg/kg) may be substituted

Alternative Parenteral Regimen

- Ampicillin/sulbactam 3 g IV Q6H + doxycycline 100 mg PO BID

Women who are started on oral antibiotics but do not respond within 72 hours should be reevaluated to confirm the diagnosis of PID and should be administered parenteral therapy on either an outpatient or inpatient basis. Patients who are treated with parenteral antibiotics usually can be transitioned to oral antibiotics within 24 hours of clinical improvement.

Follow-Up

- Patients should show significant clinical improvement within 3 days of initiation of therapy (e.g., improvement in fever, abdominal tenderness, and uterine, adnexal, and cervical motion tenderness). If the patient has not improved, consider hospitalization, additional diagnostic testing, or surgical intervention. Patients who are hospitalized for treatment initially may be switched to an oral regimen and be discharged on oral therapy after they have improved clinically.
- Evaluate sex partners and offer them treatment if they had sexual contact with the patient during the 60 days preceding the patient's onset of symptoms. Treat empirically for both chlamydia and gonorrhea.
- If the GC or CT test results are positive, rescreening for GC and CT 3 months after therapy is recommended. Provide education about sexual risk reduction. Instruct patients

to use condoms with every sexual contact to prevent reinfection with GC and CT, to prevent other STDs, and to prevent passing HIV to sex partners.

- Studies of patients treated for CT infection show reinfection rates as high as 13% within 4 months of treatment, highlighting the need for follow-up and partner treatment.

alcohol in the capsules; advise patients to contact the clinic if nausea and vomiting occur.

Patient Education

- Instruct patients to take all of their medications. Advise patients to take medications with food if they feel nauseated, and to contact the clinic promptly if they experience vomiting or are unable to take their medications.
- Sex partners from the previous 60 days need to be tested for CT, GC, and syphilis (as well as HIV, if uninfected) and treated empirically, as soon as possible, with a regimen effective against GC and CT, even if they have no symptoms. Advise patients to inform their partners that they need to be tested and treated. Otherwise, they may be reinfected.
- Advise patients to avoid sexual contact until the infection has been cured.
- Provide education about sexual risk reduction. Instruct patients to use condoms with every sexual contact to prevent becoming reinfected, to prevent other STDs, and to prevent passing HIV to sex partners.
- Advise patients that PID can recur, and that they should contact the clinic if symptoms such as pain or fever develop.
- Patients must not drink beer, wine, or any other alcoholic beverage while taking metronidazole, and for at least 24-48 hours after the last dose. Metronidazole may cause a disulfiram-like reaction, resulting in severe nausea and vomiting. Note that patients taking ritonavir capsules may experience symptoms caused by the small amount of

Pneumocystis Pneumonia

Background

Pneumocystis jiroveci pneumonia (previously called *Pneumocystis carinii* pneumonia, and still abbreviated PCP), is caused by an unusual fungus, *P. jiroveci*. Many humans appear to be infected in childhood, but clinical illness occurs only in people with advanced immunosuppression, either through new infection or reactivation of latent infection. More than 90% of PCP cases occur in patients with CD4 counts of <200 cells/ μ L. Cases of PCP in otherwise healthy young men who have sex with men were among the first recognized manifestations of AIDS, in 1981. The organism can affect many organ sites, but pneumonia is by far the most common form of disease. In the United States, the incidence of PCP has declined sharply since the use of prophylaxis and effective antiretroviral therapy (ART) became widespread, but PCP is still many patients' initial presenting opportunistic infection, and it is a significant cause of morbidity and mortality among HIV-infected patients.

S: Subjective

The patient reports fever, shortness of breath, particularly with exertion, nonproductive cough, night sweats, weight loss, or fatigue. Typically, the symptoms worsen over the course of days to weeks. Pleuritic pain and retrosternal pain or burning also may be present. There may be minimal symptoms early in the disease course of PCP.

Ask the patient about fever, fatigue, and weight loss, which may be present for weeks, with gradual worsening of shortness of breath. PCP may present less commonly with acute onset symptoms of fevers, chills, sweats, dyspnea, and cough.

Note: Given the possibility of HIV-associated tuberculosis (TB), patients with cough should be kept in respiratory isolation until TB is ruled out.

O: Objective

Perform a full physical examination, with particular attention to the following:

- Vital signs, including temperature, heart rate, blood pressure, respiratory rate, oxygen saturation at rest and after exertion (there is often a sharp drop in oxygen saturation with exertion)

- Appearance

- Lung examination

Patients may appear relatively well, or acutely ill. Tachypnea may be pronounced, and patients may exhibit such a high respiratory rate (e.g., >30 breaths per minute) that they are unable to speak without stopping frequently to breathe. Chest examination may be normal, or reveal only minimal rales, although coughing is common on deep inspiration. Cyanosis may be present around the mouth, in the nail beds, and on mucous membranes. Cough is either unproductive, or productive of a thin layer of clear or whitish mucus.

A: Assessment

A partial differential diagnosis includes the following:

- Pneumococcal pneumonia
- Other bacterial pneumonias
- TB
- Influenza Lymphocytic interstitial pneumonitis
- Bronchitis
- Cytomegalovirus (CMV) pneumonitis
- Histoplasmosis

- Other fungal pneumonia, especially cryptococcosis
- Pulmonary Kaposi sarcoma
- *Mycobacterium avium* complex
- Asthma, chronic obstructive pulmonary disease
- Congestive heart failure
- Pulmonary hypertension

P: Plan

Diagnostic Evaluation

- **CD4 cell count:** Check records for a recent CD4 count (CD4 is <200 cells/ μ L in $>90\%$ of PCP cases). Note that a CD4 count obtained in the setting of acute illness (e.g., when the patient presents with pneumonia) may be substantially lower than the usual baseline, and may be difficult to interpret.
- **Pulse oximetry at rest and after exercise:** Oxygen desaturation with exercise suggests an abnormal alveolar-arterial O_2 gradient (A-a gradient).
- **Arterial blood gas (ABG):** Hypoxemia is common, as is elevation in A-a gradient. Generally, PO_2 levels and A-a gradient are associated with disease severity. Poorer outcomes are seen with $PO_2 <70$ mm Hg and A-a gradient >35 mm Hg.
- **Lactate dehydrogenase (LDH):** Elevated serum LDH (>300 - 500 IU/L) is common.
- **Chest X-ray:** Typically shows bilateral interstitial infiltrates, but atypical patterns with cavitation, lobar infiltrates, nodules, or pneumothorax may occur, and chest X-ray findings may be normal in some cases. Upper-lobe predominance is common if the patient is receiving aerosolized pentamidine for PCP prophylaxis.
- **Thin-section chest computed tomography (CT) scan:** May show patchy ground-glass opacities; in a patient with clinical signs or symptoms of PCP, these are suggestive but not diagnostic of PCP.
- **Sputum induction:** The patient inhales saline mist to mobilize sputum from the lungs. The respiratory therapist collects expectorated sputum, which is stained and examined for *P. jiroveci* organisms. This technique is useful because of its noninvasive approach, but it requires an experienced technician, and is not available at all centers. Sensitivity varies widely (10-95%), depending on the expertise level of the staff at a particular center. (If there is any chance that the patient has TB, sputum induction should be performed in a confined space in a negative pressure area or near an exhaust fan vented safely outside, and samples should be sent for acid-fast bacilli [AFB] smear and culture.)
- **Bronchoscopy with bronchoalveolar lavage (BAL):** Definitive diagnosis usually can be made through detection of organisms in BAL fluid obtained during bronchoscopy. Sensitivity is $>95\%$ at centers with an experienced staff. BAL fluid can be evaluated for bacteria, mycobacteria, and fungi, as well as for *P. jiroveci*. Polymerase chain reaction (PCR) testing increasingly is used; its specificity has not been well established.
- **Transbronchial biopsy:** May be performed if BAL is not diagnostic and if lung disease is progressive despite treatment, to look for diagnoses other than PCP. Open lung biopsy rarely is performed.

Treatment

Presumptive treatment often is initiated on the basis of clinical presentation, chest X-ray findings, and ABG results, while definitive diagnostic tests are pending. The standard and alternative treatment regimens are shown below. Duration of treatment is 21 days for all regimens.

Trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim, Septra, cotrimoxazole) is the drug of choice, administered IV or PO for 21 days (a typical PO dose is 2 double-strength tablets taken TID). Adverse effects of TMP-SMX (e.g., rash, fever, leukopenia, anemia, gastrointestinal intolerance, hepatotoxicity, hyperkalemia) are common, mostly mild, and usually “treated through” successfully. Patients who have had previous reactions to sulfa drugs also may be desensitized successfully (see chapter *Sulfa Desensitization*). TMP-SMX

requires dosage adjustment for patients with renal insufficiency.

Pentamidine has similar efficacy to TMP-SMX but greater toxicity (nephrotoxicity, pancreatitis, glucose dysregulation, cardiac arrhythmias). It usually is reserved for patients with severe disease who require IV therapy.

Adjunctive corticosteroids

Adjunctive corticosteroids should be given if the patient's PO_2 is <70 mm Hg (breathing room air) or the A-a gradient is ≥ 35 mm Hg. Corticosteroids should be given as early as possible (preferably before or with the first dose of antibiotic therapy) and within 36-72 hours of the start of anti-PCP therapy:

- Prednisone 40 mg BID days 1-5; 40 mg QD on days 6-10; 20 mg QD on days 11-21. Alternatively, IV methylprednisolone can be given, at 75% of the prednisone dosage.

Moderate to Severe PCP
Preferred therapy <ul style="list-style-type: none">• TMP-SMX (TMP 15-20 mg/kg/day + SMX 75-100 mg/kg/day) IV in divided doses Q6H or Q8H (switch to PO after clinical improvement) Alternative therapy <ul style="list-style-type: none">• Pentamidine 4 mg/kg IV QD (dosage reduction to 3 mg/kg QD may be needed if toxicities develop)• Clindamycin 600 mg IV or 900 mg IV Q8H (or 300 mg PO Q6H or 450 mg PO Q8H) + primaquine* base 30 mg PO QD
Mild to Moderate PCP
Preferred therapy <ul style="list-style-type: none">• TMP-SMX (TMP 15-20 mg/kg/day + SMX 75-100 mg/kg/day) PO, in divided doses TID• TMP-SMX double-strength (DS), 2 tablets TID Alternative therapy <ul style="list-style-type: none">• Dapsone* 100 mg PO QD + TMP 15 mg/kg/day PO in 3 divided doses• Clindamycin (300 mg PO Q6H or 450 mg PO Q8H) + primaquine* base 30 mg PO QD• Atovaquone 750 mg PO BID with food

* Test for G6PD deficiency before use (most common among patients of African or Mediterranean descent); caution with use in patients with G6PD deficiency.

Other therapy notes

- Patients started on IV therapy can be switched to a PO treatment regimen to complete the 3-week course when they are afebrile, have improved oxygenation, and are able to take oral medications.
- For patients not already on ART, ART generally should be started within 2 weeks of initiating treatment for PCP.
- Paradoxical worsening of PCP resulting from presumed immune reconstitution inflammatory syndrome (see chapter *Immune Reconstitution Inflammatory Syndrome*) has been reported; monitor patients for worsening symptoms after ART initiation.
- Consultation with HIV experts is advisable when initiating of ART in the setting of PCP.

Treatment failures

The average time to clinical improvement for hospitalized patients is 4-8 days, so premature change in therapy should be avoided. For patients who fail to improve on appropriate therapy, it is important to exclude other diagnoses, rule out fluid overload, and consult an infectious disease specialist.

Secondary Prophylaxis

Anti-PCP prophylaxis (chronic maintenance therapy) should be given to all patients who have had an episode of PCP. Prophylaxis should be continued for life, unless immune reconstitution occurs as a result of ART and the CD4 count has been >200 cells/ μ L for more than 3 months.

In patients with stable CD4 count of >200 cells/ μ L on effective ART, it is recommended that PCP prophylaxis be discontinued because it offers little clinical benefit but may cause drug toxicity, drug interactions, and selection of drug-resistant pathogens, plus it

adds to the cost of care and to the patient's pill burden.

If PCP occurred at a CD4 count of >200 cells/ μ L, it is recommended to continue prophylaxis for life despite immune reconstitution; however, data to support this approach are limited.

Prophylactic therapy

Preferred:

- TMP-SMX DS, 1 tablet PO QD, or 1 single-strength tablet PO QD

Alternative:

- TMP-SMX DS: 1 tablet PO TIW (e.g., Monday, Wednesday, Friday)
- Dapsone* 100 mg PO QD, or 50 mg PO BID
- Dapsone* 50 mg PO QD + pyrimethamine 50 mg PO once weekly + leucovorin 25 mg PO once weekly
- Dapsone* 200 mg PO + pyrimethamine 75 mg + leucovorin 25 mg, all once weekly
- Aerosolized pentamidine 300 mg once monthly, via Respigard II nebulizer (note: does not prevent toxoplasmosis) (Warning: May increase the risk of extrapulmonary pneumocystosis, pneumothorax, and bronchospasm.)
- Atovaquone 1,500 mg PO QD (with or without pyrimethamine 25 mg PO QD + leucovorin 10 mg PO QD)

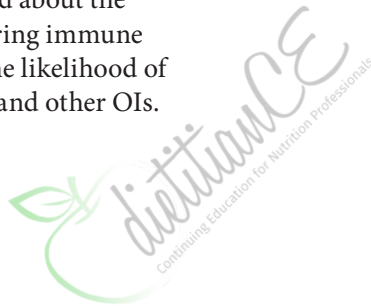
* Use with caution in G6PD deficiency.

Primary Prophylaxis

- Primary prophylaxis against PCP should be given to all HIV-infected patients with a CD4 count of <200 cells/ μ L, CD4 percentage of $<14\%$, or a history of oral candidiasis; see chapter *Opportunistic Infection Prophylaxis*.

Patient Education

- Patients should be instructed to take all medications exactly as prescribed.
- Patients should call their health care provider if symptoms worsen.
- Patients being treated with TMP-SMX or dapsone who develop rash, fever, or other new symptoms should call their provider to be evaluated for a drug reaction.
- Patients should understand that taking anti-PCP prophylaxis is extremely important for preventing repeat episodes of illness. Patients should not stop taking these medicines without talking with their health care provider, and should not let their supply of medications run out.
- Patients should be counselled about the importance of ART in restoring immune system function to reduce the likelihood of illness and death from PCP and other OIs.



Progressive Multifocal Leukoencephalopathy

Background

Classic PML

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system (CNS) caused by reactivation of latent infection with JC virus, a polyomavirus that infects and lyses oligodendrocytes. Demyelination can occur along any part of the white matter, and often does so at multiple sites (hence the term multifocal). The severity of symptoms increases as demyelination progresses.

Among HIV-infected patients, PML occurs classically and most frequently in those with CD4 counts of <200 cells/ μL who are not receiving antiretroviral therapy (ART), but it can occur in patients with higher CD4 counts and in those on suppressive ART. Patients typically present with multiple focal deficits of the cerebrum and brainstem, such as cognitive decline, focal weakness, and cranial nerve palsies, with one focal deficit often predominating. Symptoms typically progress over the course of several weeks. Imaging studies show noninflammatory, nonenhancing white matter lesions, without mass effect, with an anatomical location that maps to deficits on the neurological examination. A presumptive diagnosis of PML often can be made on the basis of the patient's clinical presentation and results of neuroimaging studies. Cerebrospinal fluid (CSF) often tests positive for JC virus DNA by polymerase chain reaction (PCR), although brain biopsy is sometimes needed for definitive diagnosis.

Among untreated patients, the interval between the first manifestation of neurologic symptoms and death may be as short as 3-4 months. Although the prognosis for patients with PML has improved with the use of potent ART, there is no specific treatment for PML, and mortality rates remain high. Patients who survive PML are likely to have permanent neurologic deficits.

Inflammatory PML

Whereas PML in the absence of ART usually is not an inflammatory condition, initiation of ART may cause an immune reconstitution inflammatory syndrome, involving new or worsening neurologic deficits and inflammatory changes seen on brain imaging and biopsy specimens. (See chapter *Immune Reconstitution Inflammatory Syndrome*.) The initiation of ART in a patient with late-stage HIV-related disease may even reveal previously undetected PML. Although many patients with inflammatory PML improve or at least stabilize, some suffer exacerbation of symptoms, rapid progression of disease, cerebral edema, herniation, and death.

S: Subjective

The patient or a caregiver may note symptoms such as weakness, gait abnormalities, difficulties with speech, visual changes, altered mental status, personality changes, and seizures. Hemianopia, ataxia, dysmetria, and hemiparesis or hemisensory deficits often are seen. The onset is likely to be subacute, with progression over the course of weeks, though neurologic disturbances may become profound. PML is not associated with headache or fever (except in cases of immune reconstitution PML); this may help to distinguish it from other opportunistic illnesses of the CNS.

O: Objective

- Measure vital signs.
- Perform a full physical examination, including a thorough neurologic and mental status evaluation. Look for focal or nonfocal neurologic deficits, particularly cranial nerve abnormalities, visual field defects, weakness, gait abnormalities, and abnormalities in cognitive function, speech, or affect; deficits are likely to be multiple. The patient typically is alert.
- Review previous laboratory values, particularly CD4 count (usually <200 cells/ μ L in patients with PML).

A: Assessment

Rule out other causes of the patient's neurologic changes. A partial differential diagnosis includes the following:

- CNS lymphoma
- Toxoplasmosis
- HIV encephalopathy
- HIV dementia
- Other (non-HIV) forms of dementia
- Cerebrovascular disease
- Neurosyphilis
- CNS opportunistic infection (e.g., tuberculosis, cryptococcosis, and cytomegalovirus)
- Multiple sclerosis

P: Plan

Diagnostic Evaluation

Presumptive diagnosis of PML often is made on the basis of clinical presentation, brain imaging, and laboratory tests.

Definitive diagnosis requires detection of JC virus DNA in CSF of patients with radiographic and clinical findings consistent with PML or a brain biopsy and identification of characteristic pathological changes. Definitive diagnosis should be attempted in all patients, if possible, and particularly in those patients for whom the diagnosis is unclear.

Radiographic Studies

CNS imaging may reveal changes typical of PML, but is nonspecific. Magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) for detecting PML. Classic PML presents as single or multiple hypodense lesions in the subcortical white matter, with no surrounding edema. On MRI, lesions show increased T2 signal and little or no enhancement with gadolinium. On CT, PML lesions typically are nonenhancing. In some patients, and particularly in

patients taking ART, PML lesions may show inflammatory changes, such as enhancement, and there may be cerebral edema.

CSF Evaluation

- CSF cell count, protein level, and glucose level generally are normal or show mild pleocytosis and slightly elevated protein.
- JC virus PCR assays are approximately 75-85% sensitive (lower in patients on ART); detection of JC virus in a patient whose clinical presentation and radiographic imaging results are consistent with PML is adequate to make a diagnosis. A negative result with JC virus PCR does not rule out PML.

Other Studies

- Other diagnostic tests should be performed as indicated to rule out other potential causes of the patient's symptoms.
- A brain biopsy should be considered if the diagnosis is unclear.

Treatment

- There is no specific treatment for JC virus. Potent ART with maximal virologic suppression and effective immune reconstitution is the only treatment that may be effective for patients with PML. Even with ART, however, mortality rates approach 40-50%, and neurologic deficits are unlikely to be reversed.
- Initiate ART for patients who are not already receiving treatment. It is not clear whether antiretroviral agents with good CNS penetration are more effective than those that are less likely to cross the blood-brain barrier.
- For patients who are on ART with incomplete virologic suppression, change the ART regimen appropriately to achieve virologic suppression, if possible. (See chapter *Antiretroviral Therapy*.)

- If symptoms are caused by immune reconstitution, consider adding corticosteroids (e.g., dexamethasone or methylprednisolone) to help decrease inflammation.
- The following agents have been proposed as specific therapy for PML, but have not been shown to be effective by prospective studies and are not recommended for treatment: cidofovir, cytarabine, and topotecan. Few data exist to assess the potential benefit of interferon-alfa and inhibitors of the serotonergic 5-HT_{2a} receptor.
- Depending on the patient's cognitive and physical status, he or she may need a care provider in the home to assure that medications are taken on schedule.
- The patient is likely to need supportive care for personal hygiene, nutrition, safety, and prevention of accidents or injury; refer as indicated.

Patient Education

- Most patients diagnosed with PML will need supportive treatment for an undetermined period of time, and hospice referral should be considered if the patient does not show clinical improvement in response to ART.
- If the patient is receiving ART, be sure that caregivers, family members, and friends are taught about the medications and are able to help the patient with adherence.
- When a diagnosis of PML has been established or suspected, initiate a discussion of plans for terminal care (including wills, advanced directives, and supportive care and services) with the patient and family members or caregivers.

Seborrheic Dermatitis

Background

Seborrheic dermatitis is one of the most common skin manifestations of HIV infection. It occurs in 3-5% of the general HIV-uninfected population but in up to 85-95% of patients with advanced HIV infection. Among HIV-infected individuals, seborrheic dermatitis often begins when their CD4 counts drop to the 450-550 cells/ μ L range. The disease is more likely to occur among young adults (because they have oilier skin) and males, and is more common in areas with cold, dry winter air. It is rarely found in African blacks, unless the person is immunocompromised. It is more common during times of mental stress and severe illness.

Seborrheic dermatitis is a scaling, inflammatory skin disease that may flare and subside over time. It is characterized by itchy reddish or pink patches of skin, accompanied by greasy flakes or scales. It most commonly occurs in the scalp and on the face, especially at the nasolabial folds, eyebrows, and forehead, but also may develop on the ears, chest, upper back, axillae, and groin. Dandruff is considered to be a mild form of seborrheic dermatitis. Occasionally, seborrheic dermatitis may be severe, may involve large areas of the body, and may be resistant to treatment. Severe manifestations are more likely with advanced HIV infection.

The etiology of seborrheic dermatitis is not entirely clear. *Malassezia* yeast (formerly called *Pityrosporum ovale*), a fungus that inhabits the oily skin areas of 92% of humans, is the most likely culprit. This same yeast also is thought to cause tinea versicolor and *Pityrosporum* folliculitis. Overgrowth of the *Malassezia* yeast in the oily skin environment, failure of the immune system to regulate the fungus, and the skin's inflammatory reaction to the yeast overgrowth appear to be the chief factors that cause the dermatitis.

S: Subjective

The patient complains of a new rash, sometimes itchy, or of "dry skin" that will not go away despite the application of topical moisturizers.

O: Objective

Perform a thorough evaluation of the skin with special attention to the scalp, medial eyebrows, eyelashes and eyelids, beard and other facial hair areas, nasolabial folds, postauricular areas, the concha of the auricle, glabella, umbilicus, central chest, back, axillae, and groin. Seborrheic dermatitis appears as white to yellow greasy or waxy flakes over red or pink patches of skin; however, discrete fine scales may indicate a mild form of the

disease. Around the eyes, seborrheic dermatitis can cause eyelid erythema and scaling. The distribution usually is symmetrical.

A: Assessment

The diagnosis of seborrheic dermatitis is based on the characteristic appearance. A partial differential diagnosis includes psoriasis, atopic dermatitis, contact dermatitis, erythrasma, tinea capitis (can be present on the scalp without hair loss), rosacea, and rarely, dermatomyositis.

P: Plan

Treatment

- Initiate antiretroviral therapy (ART) for patients not on ART

- Specific treatments are divided into three types: antimycotic (first choice), antiinflammatory (second choice), and keratolytic. Shampoos may be used on the entire body, with avoidance of eyes and mucous membranes.
- Topical antifungal medications: The azoles and ciclopirox have been well studied and shown to have both antifungal and antiinflammatory activity. Various preparations are available; selection can be based on cost and availability. Antifungals may be used in combination with topical corticosteroid therapy (see below). Effective antifungals include but are not limited to the following:
 - Ketoconazole (Nizoral) 2% cream or shampoo; ketoconazole is one of the most widely studied of all topical treatments
 - Bifonazole ointment, miconazole cream (Monistat), terbinafine (Lamisil) 1% solution or cream, or clotrimazole (Lotrimin) 1% cream, lotion, or solution
 - Ciclopiroxolamine (Loprox) 1% shampoo, gel, or cream
 - Zinc pyrithione (keratolytic/antifungal) shampoo or cream
- Topical corticosteroids generally are effective and may be used in combination with topical antifungal therapy (see above). Low-potency agents (e.g., hydrocortisone 1%) rather than high-potency corticosteroids (e.g., betamethasone dipropionate, triamcinolone), are recommended, especially for the face, to reduce the risk of adverse effects associated with all corticosteroids (e.g., atrophy, telangiectasias, and perioral dermatitis). Corticosteroid shampoos also may be considered for scalp involvement.
- Selenium sulfide/sulfur preparations (the most common is selenium sulfide shampoo).
- Whole coal tar, crude coal tar extract: shampoos, creams, and gels.
- Lithium succinate or lithium gluconate ointment, available in some countries as a combination of lithium succinate 8% and zinc sulfate 0.05% (may have antifungal or antiinflammatory effects). Not for use on the scalp.
- Honey, 90% diluted with warm water, may be used to treat seborrheic dermatitis and dandruff.
- Azelaic acid, 15% gel or 20% cream, has sebosuppressive, antimicrobial, antifungal, and antiinflammatory activity (also used for acne and rosacea).
- Noncorticosteroid topical immunomodulators (calcineurin inhibitors):
 - Tacrolimus
 - Pimecrolimus
- Oral therapy may be used for patients who are refractory to topical treatment (may interact with protease inhibitors and nonnucleoside reverse transcriptase inhibitors; check for possible drug-drug interactions with antiretroviral and other medications before prescribing). There are limited data regarding the efficacy of systemic medication.
 - Fluconazole 300 mg once weekly for 2 weeks
 - Itraconazole 200 mg QD for 7 days
 - Ketoconazole 200 mg QD for no more than 4 weeks
 - Terbinafine 250 mg QD for 4 weeks

Potential adverse effects:

- With all topical products: skin burning, stinging, dryness; allergic or contact dermatitis. Tar shampoos may discolor light hair, leave an oily film on hair, and leave an odor. Coal tar may be carcinogenic; use shampoo no more than twice a week, leave on skin or hair for 5 minutes, and rinse well.
- Topical corticosteroids may cause skin atrophy, telangiectasias, folliculitis, striae, and excessive hair growth. Risk of adverse effects can be mediated by using product infrequently, diluting the product, or limiting the amount of time the product is on the skin.
- With oral therapy, monitor for hepatotoxicity.

Patient Education

- Although topical and oral medicines can relieve symptoms, recurrence is common. Effective antiretroviral therapy should be considered to control the effects of HIV on the immune system and thereby decrease exacerbations and the severity of seborrheic dermatitis associated with immunosuppression.

Sinusitis

Background

Sinusitis is defined as an inflammation involving the membrane lining of any sinus, and it occurs more frequently in people with HIV infection than in the general population. It commonly occurs as part of a viral upper respiratory infection (URI), and usually is self-limited. Bacterial sinusitis usually occurs as a secondary complication of a viral URI, which causes decreased patency of the nasal ostia, decreased nasal ciliary action, and increased mucus production. Acute sinusitis is defined as lasting up to 4 weeks, whereas chronic sinusitis persists for at least 12 weeks.

HIV-infected patients are susceptible to sinusitis for a number of reasons related to their immunosuppression. Pathophysiologic mechanisms for this susceptibility may include proliferation of lymphatic tissue contributing to nasal obstruction, defects in B-cell and T-cell immunity owing to HIV, and defects in production of immunoglobulins, specifically IgE, resulting in an exaggerated allergic response in the nasal mucosa. As in the general population, the most common pathogens causing acute bacterial sinusitis are *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*. However, HIV-infected patients have a greater incidence of sinusitis caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The bacterial causes of chronic sinusitis are not well defined, but may involve more polymicrobial and anaerobic infections. In patients with severe immunosuppression, particularly those with CD4 counts of ≤ 50 cells/ μ L, sinusitis may be caused by *Aspergillus* and other fungal pathogens.

S: Subjective

The patient may complain of facial pain, frontal or maxillary headache, postnasal drip, or fever.

Ask the patient about specific symptoms, the duration and progression of symptoms, and treatments attempted.

- Fever
- Facial pain or pressure, headache; positional pain (worse when patient bends forward)
- Purulent or bloody nasal discharge
- Postnasal drip
- Nasal congestion
- Recent URI
- Malaise
- Chronic cough

- Maxillary tooth pain
- Ear pressure
- History of chronic sinusitis, seasonal allergies, antibiotic allergies, atopy
- Tobacco use, inhaled recreational drugs

O: Objective

- Document vital signs.
- Perform a careful physical examination focusing on the head and face, neck, and lungs. Examine the nose, mouth, ears, and sinuses.
 - Look for nares inflammation and drainage from sinus ostia.
 - Examine the tympanic membranes and external auditory canals.

- Evaluate the oropharynx for mucus drainage, lesions, and exudates.
- Check the teeth and gums for tenderness and erythema.
- Palpate for tenderness over frontal and maxillary sinus cavities.
- Examine the face and orbits for swelling or erythema.
- Perform cranial nerve examination.
- Auscultate the chest for abnormal lung sounds.

A: Assessment

A partial differential diagnosis includes the following:

- Allergic rhinitis
- Sinus blockage by other lesions such as Kaposi sarcoma or lymphoma (particularly if the CD4 count is <200 cells/ μL) or fungal infections (if the CD4 count is <50 cells/ μL)
- Dental abscess, caries
- Meningitis
- Vasculitis
- Trauma

P: Plan

Diagnostic Evaluation

Uncomplicated acute sinusitis usually is a clinical diagnosis. There are no symptoms, physical findings, or tests that reliably distinguish bacterial from viral sinusitis. Patients generally can be assumed to have bacterial sinusitis if symptoms do not resolve, or if they worsen, over the course of 7-10 days. Any patient with high fever or severe or unusual symptoms should be evaluated urgently for other causes of illness.

Imaging studies usually are not indicated for uncomplicated acute sinusitis. In patients with a poor response to empiric antibiotic

therapy for acute bacterial sinusitis, worsening symptoms, and those with suspected chronic sinusitis, computed tomography (CT) scans of the paranasal sinuses are the best initial radiologic study. Standard X-rays (sinus series) can detect cloudiness or air-fluid levels and will show mucosal thickening (a nonspecific finding in HIV-infected individuals).

Cultures of nasal aspirates are not useful for diagnosis, because nasal fluids do not accurately represent pathogens in the paranasal sinuses. Sinus aspirate cultures will give definitive diagnosis of a specific organism in the majority of cases; this may be considered in complicated cases. Definitive diagnosis of invasive fungal sinusitis requires tissue for culture.

Treatment

Treatment is multimodal. For viral sinusitis, treatment is based on symptom suppression; for bacterial sinusitis, an antibiotic can be added to other therapies, e.g., if symptomatic treatment has not resulted in improvement after 10 days.

- Nasal irrigation with saline solution 1-2 times daily (solution should be prepared from sterile or bottled water)
- Nasal steroid (e.g., budesonide, fluticasone, mometasone, or triamcinolone) (see "Potential ARV Interactions," below)
- Nonsteroidal antiinflammatory drugs (NSAIDs): ibuprofen or other
- Mucolytic agent: guaifenesin
- Cough suppressant as needed
- Antihistamine: chlorpheniramine or other
- Decongestant: e.g., ephedrine, pseudoephedrine

If acute bacterial sinusitis is suspected (e.g., symptoms have not improved within 10 days), treat as above and add an antibiotic for a 5-7 day course of therapy:

- Amoxicillin/clavulanate (Augmentin) 825/125 mg PO BID or 500/125 mg PO TID (more effective against resistant species of pneumococcus and *H. influenza* than amoxicillin)
- Doxycycline 100 mg PO BID
- Levofloxacin 500 mg QD or moxifloxacin 400 mg QD

For chronic sinusitis, administer multimodal treatments as listed above for 3-4 weeks. The value of antibiotics in chronic sinusitis is unclear; consider especially if a trial of antibiotics has not been undertaken.

If symptoms persist or worsen, refer patients to an otolaryngologist for further evaluation and treatment.

Patient Education

- Instruct patients in the correct use of medications used to treat sinusitis, including proper technique for nasal irrigation, as required.
- Advise patients that drinking eight glasses (8-12 oz each) of fluid daily helps to keep the mucus thin enough to drain from the sinus passages.
- Instruct patients to take antibiotics on schedule until the entire prescription is gone in order to prevent recurrence of the infection. Advise patients to call or return to clinic for swelling of the face or swelling around the eyes, increased facial tenderness, new or worsening fever, or other concerning symptoms.

Potential ARV Interactions

Protease inhibitors (PIs) (particularly ritonavir-boosted PIs) or cobicistat may increase serum glucocorticoid levels if used concurrently with nasal steroids. Fluticasone (e.g., Flonase) nasal spray or inhaler should not be used with ritonavir-boosted PIs or cobicistat, and should be avoided, if possible, in patients taking unboosted PIs. Budesonide (Rhinocort Aqua) nasal spray also should be avoided with ritonavir-boosted PIs or cobicistat. Interactions between PIs or cobicistat and other nasal steroids have not been well studied, though available data suggest that beclomethasone has no clinically significant interaction with protease inhibitors.

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Syphilis

Background

Syphilis is a sexually transmitted disease (STD) caused by the spirochete *Treponema pallidum*. It is a complex disease with protean variations that can mimic many common infections or illnesses. HIV infection may alter the natural history and management of syphilis, causing a more rapid course of illness, higher risk of neurologic complications, and potentially greater risk of treatment failure with standard regimens. Because many individuals with syphilis have no symptoms, or have symptoms that subside without treatment, sexually active individuals at risk of syphilis should receive regular screening for syphilis, as well as for other STDs.

There has been a resurgence of syphilis in the United States, particularly among men who have sex with men (MSM). This trend is concerning, because syphilis can have major health consequences if it is undetected and untreated, and because it increases the risk of HIV transmission. Risk assessment should be conducted at each patient visit for unprotected sex (including oral, anal, and vaginal sex), multiple sex partners, and use of recreational drugs (methamphetamine and cocaine, in particular, are associated with high-risk sexual practices among MSM). Sexually active persons with HIV who are at risk of acquiring syphilis should be screened at least annually, as discussed below. MSM with multiple partners should be tested every 3-6 months.

The natural history of untreated syphilis infection is divided into stages based on length of infection.

Primary Syphilis

Primary syphilis usually manifests after an incubation period of 1-3 weeks from exposure and is characterized by a painless self-limiting ulcer (chancre) at the site of inoculation, which usually occurs during sexual contact. The organism disseminates shortly after exposure via the lymphatics to the bloodstream and beyond. HIV-infected individuals often have multiple or atypical syphilitic lesions that could be misidentified. Some patients have no primary lesion, or have a primary lesion that is not visible. Associated regional lymphadenopathy can occur. Without treatment, the primary lesion generally lasts a few days to a few weeks. Individuals sometimes have a resolving chancre concurrently with a rash of secondary syphilis.

Secondary Syphilis

Secondary syphilis usually develops 2-8 weeks after initial infection and is caused by ongoing replication of the spirochete at disseminated sites of infection that may involve multiple organ systems but most commonly involves the skin and mucous membranes. Rash is the most common presenting symptom; skin lesions may be macular, maculopapular, papular, or pustular, or they may appear as condyloma lata (which may look like condyloma acuminata caused by human papillomavirus). The rash often appears on the trunk and extremities and may involve the palms and soles of feet. Constitutional symptoms, lymphadenopathy, arthralgias, and myalgias are common and neurologic or other symptoms may occur. In the absence of treatment, the manifestations of secondary syphilis last days to weeks, then usually resolve to the latent stages.

HRSA HAB Performance Measures

Percentage of adult patients with a diagnosis of HIV who had a **test for syphilis** performed within the measurement year

(Adult and Adolescent measure)

Latent Syphilis

Latent syphilis follows resolution of secondary syphilis. As in HIV-uninfected individuals, latent syphilis is asymptomatic and the diagnosis is determined by positive serologic tests. Latent syphilis is further classified as “early latent” if the infection is known to be <1 year in duration, “late latent” if the infection is known to be >1 year in duration, or “latent syphilis of unknown duration” if the duration of infection is not known.

Late or Tertiary Syphilis

Late or tertiary syphilis is caused by chronic infection with progressive disease in any system causing serious illness and death in untreated patients. The most common manifestations include cardiovascular syphilis, gummatous syphilis, and the late forms of neurosyphilis (tabes dorsalis and general paresis) (see the “Neurosyphilis” section, below).

Neurosyphilis

Neurosyphilis can occur at any time after initial infection, owing to early spread of the spirochete to the central nervous system (CNS) in approximately 30-40% of patients. The vast majority of these patients has no neurologic signs or symptoms and clears this site of infection. The early forms of neurosyphilis occur within weeks to a few years after infection, including during the secondary stage of syphilis. Early neurosyphilis can manifest as syphilitic meningitis (symptoms may include headache, confusion, nausea, vomiting, and a stiff neck); cranial nerve abnormalities (particularly extraocular or facial muscle palsies, causing visual changes, and facial weakness, tinnitus, and hearing loss) also may be present. The second manifestation of early neurosyphilis is meningovascular syphilis, which presents with stuttering stroke symptoms owing to increasing inflammation of the cerebral arteries causing intermittent occlusion. Ocular syphilis (uveitis, retinitis, retinal detachment, and other eye abnormalities) may occur early after infection with or without the early forms of neurosyphilis. Although these early forms of neurosyphilis, including ocular syphilis, occur in patients without HIV, they may be more common among HIV-infected individuals.

S: Subjective

Symptoms depend on the site of initial infection, the stage of disease, and whether neurosyphilis is present. Symptoms are not present in most patients.

If symptoms are present, the patient may experience the following:

- Painless sore(s), ulcer(s), or abnormal lesions in the genital area, vagina, anus, or oral cavity
- New rash, usually on the trunk, often on extremities, soles of the feet, or palms
- Wart-like growths, mucus patches, or patchy hair loss
- Fever, malaise, swollen glands, arthralgias, myalgias

- Neurosyphilis: vision changes, eye pain, tinnitus, hearing loss, headaches, dizziness, facial weakness, motor or sensory loss, altered mental status, changes in personality or affect, lightning-rod pains in the lower extremities

Conduct a targeted history of patients at risk of syphilis, those who are contacts to a case, or those with positive syphilis serologies, asking about symptoms listed above, including duration; inquire about other or associated symptoms. Ascertain the following:

- Previous diagnosis of syphilis, stage, treatment (including facility where diagnosed and treated), and last titer result
- New sex partners in past 90 days (for primary or secondary syphilis)
- Date of last negative syphilis test, and where obtained
- Pregnancy status

O: Objective

Check for fever, document other vital signs.

Perform a complete examination including the following:

- Skin and mucosal areas (including the palms and soles, genitals, perianal area): chancre/ulcers, abnormal lesions, rash, condyloma lata, patchy hair loss
- Oropharynx: chancres, mucus patches, condyloma lata
- Lymph nodes
- Ophthalmic examination (including slit-lamp examination for persons with ocular complaints; uveitis, retinitis, retinal detachment)
- Neurologic examination (mental status, cranial nerves [including visual acuity], sensory, motor, reflexes, coordination, gait): abnormal mental status, visual acuity changes, extraocular movement abnormalities, neurosensory hearing loss, facial palsy, paraesthesias, sensory or motor loss, hyperactive reflexes, ataxia

A: Assessment

Because syphilis has a wide range of manifestations, the differential diagnosis is broad. It is important to consider syphilis as a possible cause of many presenting illnesses. A partial differential diagnosis includes the following:

- Other causes of maculopapular rashes: pityriasis, tinea versicolor, drug eruption, folliculitis, scabies, psoriasis, acute HIV infection
- Other causes of genital ulcerative disease: herpes simplex virus (HSV), chancroid, trauma, other skin infections (e.g., those caused by *Staphylococcus* or *Candida*)
- Other causes of ocular disease: cytomegalovirus (CMV) retinitis, CMV immune reconstitution uveitis, HSV keratitis

- Other causes of neurologic disease: Bell palsy, CNS lymphoma, toxoplasmosis, other causes of meningitis, stroke
- Other causes of systemic symptoms (e.g., fever, malaise, adenopathy): acute HIV infection, acute hepatitis, other infections or malignancies

P: Plan

Diagnostic Evaluation

Darkfield examination and direct fluorescent antibody

Darkfield examination, direct fluorescent antibody (DFA), or polymerase chain reaction (PCR) testing of a sample from suspicious genital or anal chancres or moist dermatologic lesions (not oral lesions) are definitive tests for syphilis, although these are not available in most clinic settings.

Serologic tests

Nontreponemal tests (rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL]) traditionally have been used as initial serologic tests for syphilis. Because false-positive results may occur, particularly in the setting of HIV infection, positive nontreponemal test results must be confirmed with a treponemal test. Treponemal antibody tests (TP-PA [*T. pallidum* particle agglutination], EIA [enzyme immunoassay], or CIA [chemiluminescence immunoassay]) should be used to confirm a positive nontreponemal test. Many high-volume laboratories have begun to use a treponemal test as an initial screen for syphilis infection, followed by a quantitative nontreponemal test, to reduce the workload from the titration required for nontreponemal titers. The FTA-ABS (fluorescent treponemal antibody absorption) may lack specificity and is no longer recommended as the gold standard treponemal test.

Nontreponemal tests may be falsely negative in primary and secondary syphilis, before a sufficient antibody response has developed;

treponemal tests may be slightly more sensitive and should be ordered if the nontreponemal test result is negative in a patient with signs or symptoms suggestive of primary or secondary syphilis. Another possible cause of a false-negative nontreponemal result is the prozone phenomenon, seen when antibody concentrations are very high (usually in secondary syphilis) and the specimen is not diluted sufficiently. If serologic test results are negative and suspicion of syphilis is high, request that the laboratory perform additional dilutions on nontreponemal test specimens; if the diluted serum is nonreactive, perform other diagnostic tests (e.g., biopsy).

A nontreponemal test titer should be obtained on the day of treatment to use in determining response to treatment; a fourfold change in titer is considered a significant change. Although fluctuating titers after treatment in HIV-infected patients have been seen, a sustained (>2 weeks) fourfold increase in titer raises concerns about reinfection or treatment failure. Note that the same nontreponemal test should be used consistently for a single patient; RPR titers cannot be compared with VDRL titers.

Cerebrospinal fluid evaluation

HIV-infected patients with neurologic or ocular signs or symptoms of syphilis or tertiary syphilis should undergo lumbar puncture (LP) for cerebrospinal fluid (CSF) analysis. CSF evaluation also is indicated for patients in whom treatment for early syphilis fails (see below). Routine CSF evaluation is not indicated for HIV-infected patients who have syphilis without neurologic or ophthalmic signs or symptoms. CSF analysis should include the following:

- CSF-VDRL: This test is specific but not very sensitive; a positive result is diagnostic but a negative result does not rule out neurosyphilis.
- Leukocytes: Elevated white blood cell count (>10 cells/ μ L) is suggestive but not specific. Note that mononuclear pleocytosis (up to

5-20 cells/ μ L) is not uncommon in patients with HIV infection, particularly those with higher CD4 cell counts; a threshold of >20 cells/ μ L may improve the specificity of the neurosyphilis diagnosis.

- Some recommend checking CSF FTA-ABS. This is very sensitive but not very specific; a negative result indicates that neurosyphilis is highly unlikely.

Other testing

All patients who test positive for syphilis should be tested for gonorrhea and chlamydia, with sampling sites based on sexual practices and exposures (oropharyngeal, urethral, cervical or vaginal, or anorectal testing). Patients not known to be HIV infected also should be tested for HIV.

Treatment

Treatment of syphilis in HIV-infected individuals essentially is the same as in HIV-uninfected individuals, and depends on stage and the presence or absence of neurosyphilis. It is important to follow patients closely to assure the success of treatment. For further information, see the Centers for Disease Control and Prevention (CDC) STD treatment guidelines or the CDC/NIH/IDSA opportunistic infection (OI) guidelines (see “References,” below).

An RPR or VDRL test should be sent on the day of treatment; the titer will be the reference point for assessing treatment efficacy (see “Follow-Up,” below).

Early syphilis

(<1 year in duration [i.e., primary, secondary, and early latent]; no neurologic signs or symptoms)

- **Preferred therapy:** benzathine penicillin G, 2.4 million units IM (single dose)

- **Alternative therapy:** (for patients with penicillin allergy) note that penicillin is strongly preferred; consider allergy testing and desensitization to penicillin; alternative therapies are not as well proven in HIV-infected individuals; close monitoring for treatment response is recommended

- Doxycycline 100 mg PO BID for 14 days
- Tetracycline, 500 mg PO QID for 14 days*
- Ceftriaxone, 1 g IM or IV QD for 10-14 days

* Proposed in the STD guidelines; not mentioned in the OI guidelines

Treatment failures and resistance have been reported in patients treated with azithromycin (2 g, single dose); the STD and OI guidelines state that this regimen should not be used to treat MSM or pregnant women. For other patients, both guidelines state that azithromycin should be considered only when treatment with penicillin or doxycycline is not feasible, and with close follow-up.

Late latent syphilis

(>1 year in duration or of unknown duration, no neurologic signs or symptoms)

- **Preferred therapy:** Benzathine penicillin G, 2.4 million units IM weekly for 3 consecutive weeks (7.2 million units in total)
- **Alternative therapy:** For penicillin-allergic patients, refer for desensitization to penicillin. As an alternative, some specialists consider doxycycline 100 mg PO BID for 28 days, although efficacy in HIV-infected individuals is not proven. Referral to infectious disease specialist and close clinical monitoring are required.

Tertiary syphilis

Consult with specialists.

Neurosyphilis

(syphilis at any stage with neurologic or ocular symptoms, or CSF abnormalities consistent with neurosyphilis in patients who fail treatment)

Ideally, patients should be hospitalized and given 2 weeks of penicillin IV under close observation. Penicillin-allergic patients should be referred for desensitization, if possible.

- **Preferred therapy:** aqueous crystalline penicillin G, 18-24 million units IV per day (3-4 million units Q4H [or continuous infusion] for 10-14 days).
- **Alternative therapy (requires strict adherence with therapy):**
 - Procaine penicillin 2.4 million units IM per day, plus probenecid 500 mg PO QID, both for 10-14 days
 - Some experts consider use of ceftriaxone 2 g IM or IV QD for 10-14 days with close clinical monitoring
- Most experts recommend administration of benzathine penicillin, 2.4 million units IM weekly for 3 weeks, after completion of the standard 10- to 14-day course of therapy for neurosyphilis.
- Recheck CSF leukocyte count every 6 months until the cell count normalizes (if CSF pleocytosis was present at initial evaluation). If the leukocyte count is not lower at 6 months, consider retreatment (consult with a specialist). Normalization of serum RPR may predict normalization of CSF parameters.

Note: A **Jarisch-Herxheimer reaction** may occur after initial syphilis treatment, especially in primary, secondary, or even latent syphilis. This self-limited treatment effect should not be confused with an allergic reaction to penicillin. It usually begins 2-8 hours after the first dose of penicillin and consists of fever, chills, arthralgias, malaise, tender lymphadenopathy, and intensification of rash. It resolves within 24 hours and is best treated

with rest and acetaminophen. Patients should be warned about the possibility of a Jarisch-Herxheimer reaction.

Pregnancy

Pregnant women should be treated with penicillin, using a regimen appropriate for the stage of infection (see above). Additional treatment may be indicated in early syphilis; consult with a specialist. Penicillin-allergic pregnant women should be referred for desensitization to penicillin. Doxycycline and tetracycline may cause fetal toxicity and should not be used during pregnancy. Azithromycin and erythromycin do not have adequate efficacy in treating pregnant women or their fetuses and should not be used. The efficacy of ceftriaxone during pregnancy has not been studied adequately.

Women treated during the second half of pregnancy are at risk of contractions, early labor, and fetal distress if they develop a Jarisch-Herxheimer reaction; thus, they should be advised to seek obstetric attention if they develop fever or contractions, or note a decrease in fetal movement.

Sex partners

Syphilis is transmitted sexually only when mucocutaneous lesions of syphilis are present; this is uncommon after the first year of infection. Nevertheless, sex partners of a patient who has syphilis in any stage should be evaluated. For patients with primary syphilis, that means partners within the previous 3 months plus the duration of the lesion; for patients with secondary syphilis, partners within the previous 6 months plus the duration of signs; for patients with early latent syphilis, partners within the past 1 year.

- Persons exposed within 90 days preceding the diagnosis of primary, secondary, or early latent syphilis should be treated presumptively, as they may be infected with syphilis even if they are seronegative.
- Persons exposed more than 90 days before the diagnosis of primary, secondary, or early latent syphilis should be treated presumptively if serologic test results are not available immediately and their follow-up is in doubt. Otherwise, they should receive serologic testing and be treated appropriately if the test result is positive.

Follow-Up

All HIV-infected patients treated for early syphilis should be evaluated clinically and serologically at 3, 6, 9, 12, and 24 months (at 6, 12, 18, and 24 months for latent syphilis) to rule out treatment failure. Treatment success is determined by a fourfold decrease (equivalent to two dilutions) in RPR or VDRL titer by 6-12 months (for primary and secondary syphilis) or 12-24 months (for latent syphilis) of treatment. Patients whose titers do not decrease appropriately could have experienced treatment failure or may have been reinfected. Any patient with apparent treatment failure should undergo an LP for CSF analysis and be re-treated as appropriate.

For patients with neurosyphilis, current guidelines recommend that, if a CSF pleocytosis was present initially, the CSF cell count should be checked every 6 months until it decreases. If the CSF cell count is not normal after 2 years, retreatment for neurosyphilis should be considered.

After syphilis treatment that results in at least a fourfold decrease in RPR or VDRL titer, a sustained fourfold increase in titer most commonly reflects reinfection; the patient should be evaluated carefully for possible reexposure and treated for new infection if appropriate. If reinfection is unlikely, CSF testing should be done and appropriate treatment should be given. For patients with persistently high or fluctuating titers after CSF examination and appropriate re-treatment, consult with a specialist.

Some patients retain reactive (usually at low titer) nontreponemal test results after successful treatment for syphilis. In these “serofast” individuals, reinfection with syphilis is indicated by a rise in test titer of at least fourfold.

Risk-reduction counseling

All patients with syphilis should receive risk evaluation and risk-reduction counseling. Evaluate each patient’s sexual practices with

regard to risk of acquiring STDs and of transmitting HIV. Work with the patient to reduce sexual risks.

Patient Education

- Instruct patients to go to clinic for treatment at the intervals recommended. If patients are given oral antibiotics (penicillin-allergic individuals), instruct them to take their medications exactly as prescribed.
- Warn patients about the possibility of a Jarisch-Herxheimer reaction after an initial dose of penicillin and advise them about self-management of associated symptoms (e.g., acetaminophen or aspirin at usual doses, fluids, and rest).
- Instruct patients about the required follow-up laboratory and clinical evaluations necessary to document adequate treatment. Emphasize the need for regular evaluation of treatment efficacy.
- Sex partners from the previous 3-6 months (sometimes longer, depending on the stage of syphilis) need to be evaluated and treated as soon as possible, even if they have no symptoms. Advise patients to inform their partners that they need to be tested and treated. Ask patients whether they would like assistance with partner notification and refer to the local health department for partner services, if available.
- Syphilis is a reportable communicable disease in the United States. Inform patients that they may be contacted to verify adequate treatment and assist with partner notification and treatment.
- Provide education about sexual risk reduction. Review sexual practices and support patients in using condoms with every sexual contact to prevent becoming reinfected with syphilis or infected with other STDs, and to prevent passing HIV to sex partners.

Toxoplasmosis

Background

Toxoplasma gondii is a common intracellular protozoan that preferentially infects the central nervous system (CNS). In immunodeficient patients it may cause encephalitis; it also can cause local disease such as chorioretinitis and pneumonia. Clinical disease usually occurs through reactivation of latent infection in patients who have CD4 counts of <100 cells/ μL . *Toxoplasma* seroprevalence varies widely, from 11% in the United States to 75% in some European countries, and even higher in certain resource-limited countries. In the absence of prophylaxis, toxoplasmic encephalitis occurs in more than 30% of patients with advanced HIV infection who are seropositive for *T. gondii*. There have been case reports of CNS toxoplasmosis in the setting of immune reconstitution on antiretroviral therapy (ART); see chapter *Immune Reconstitution Inflammatory Syndrome*.

Toxoplasma has an infectious reservoir in almost all animals; humans acquire infection either through ingestion of tissue cysts contained in undercooked meat (usually pork, lamb, or beef) or oocysts on contaminated vegetables or through exposure to cat feces containing oocysts. There is no transmission by person-to-person contact.

CNS toxoplasmosis is an AIDS-defining condition that can be progressive and fatal. However, antimicrobial therapy, especially if given in conjunction with ART that results in immune reconstitution, can be successful in treating toxoplasmosis. Specific prophylaxis and effective ART also may be used to prevent toxoplasmosis in patients with advanced AIDS who have latent *T. gondii* infection (as demonstrated by the presence of anti-*Toxoplasma* immunoglobulin G [IgG] antibodies; see chapter *Preventing Exposure to Opportunistic and Other Infections*).

S: Subjective

The patient may complain of subacute onset of dull, constant headache, fever, visual changes or other focal neurologic symptoms, confusion, or disorientation. Seizures may occur. Caregivers may report subtle alterations in mental status or mood.

Take a careful history from the patient and caregivers about the symptoms listed above and their duration, progression, and severity. Inquire about other related symptoms. Ask whether the patient is taking *Toxoplasma* prophylaxis or ART.

O: Objective

- Measure vital signs (temperature, heart rate, blood pressure, respiratory rate).

- Perform a full physical examination including a thorough neurologic examination, looking for focal or nonfocal neurologic deficits, particularly weakness, cranial nerve abnormalities, visual field defects, gait disturbances, and abnormalities in speech, cognitive, or affective functions.
- Review previous laboratory values, particularly the following:
- CD4 count (usually <50 - 100 cells/ μL in patients with toxoplasmosis)
- *Toxoplasma* IgG ($>95\%$ of patients with toxoplasmosis have positive IgG)

A: Assessment

Rule out other infectious or neoplastic causes of headache, fever, and neurologic changes.

A partial differential diagnosis includes the following:

- CNS lymphoma
- Cryptococcal meningitis
- Progressive multifocal leukoencephalopathy (PML)
- Tuberculous meningitis
- Brain abscesses of bacterial, fungal, or mycobacterial etiologies
- Herpes simplex virus or cytomegalovirus (CMV) encephalitis
- Primary HIV encephalopathy
- AIDS dementia complex
- Cerebrovascular accident secondary to hemorrhage, hypoxia, or emboli from vegetative endocarditis
- Neurosyphilis
- Other causes of chorioretinitis such as CMV, HIV, and cryptosporidiosis

P: Plan

Diagnostic Evaluation

Definitive diagnosis requires identification of *T. gondii* in tissue biopsy or body fluid samples from a patient with a compatible clinical presentation. Brain biopsy usually is not performed if toxoplasmosis is strongly suspected; instead, presumptive diagnosis is made on the basis of clinical presentation, laboratory and imaging tests, and response to therapy. Brain biopsy should be considered for patients who do not respond to therapy and for those whose diagnosis is unclear.

- Serum *Toxoplasma* IgG antibody test results are positive in nearly all patients with toxoplasmic encephalitis. A negative IgG test result makes the diagnosis very unlikely but does not rule it out. (Antibody titer changes are uncommon in reactivation disease and are not useful in making a diagnosis.)

- CNS imaging with computed tomography (CT) typically shows multiple contrast-enhancing mass lesions, but may show a single lesion or no lesions. Magnetic resonance imaging (MRI) is more sensitive than CT for CNS toxoplasmosis. Other imaging studies, such as single photon emission CT (SPECT), may be useful in distinguishing toxoplasmic lesions from CNS lymphoma.
- If possible, cerebrospinal fluid should be checked for *T. gondii* by polymerase chain reaction (PCR).
- Other diagnostic tests should be performed as indicated to rule out other potential causes of the patient's symptoms.
- Patients with toxoplasmic encephalitis typically respond quickly to treatment. If clinical improvement is not seen after 10-14 days of appropriate treatment, or if clinical worsening is seen in the first week, consider brain biopsy for alternative diagnoses.

Treatment

Treatment consists of two phases: acute therapy and chronic maintenance therapy. If possible, consult with an expert on the management of toxoplasmosis.

Presumptive treatment often is begun on the basis of clinical presentation, positive *Toxoplasma* IgG, and results of brain imaging studies. If patients do not respond quickly to treatment, other diagnoses should be considered. The following recommendations are based on treatment guidelines published by the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association/Infectious Diseases Society of America (see "References," below).

Acute Therapy

Acute therapy should be given for at least 6 weeks, and until the patient has shown improvement by clinical and radiographic measures.

Preferred

- Pyrimethamine 200 mg PO as a single loading dose, then 50 mg (<60 kg body weight) or 75 mg (>60 kg body weight) QD + sulfadiazine 1,000 mg (<60 kg body weight) or 1,500 mg (>60 kg body weight) PO Q6H + folinic acid (leucovorin) 10-25 mg QD

Dosage adjustments to the lower end of therapeutic range of pyrimethamine and sulfadiazine may be considered for patients who have significant bone marrow suppression despite folinic acid supplementation. Monitor patients carefully for cytopenias, especially if they are taking other agents that cause bone marrow suppression, such as zidovudine, valganciclovir, and ganciclovir.

Note: Patients at risk of G6PD deficiency should be checked for G6PD deficiency before starting pyrimethamine.

Alternative

- Pyrimethamine + folinic acid (administered as described above) + clindamycin 600 mg PO or IV Q6H; recommended for patients with significant allergic reactions to sulfa medications
- Trimethoprim-sulfamethoxazole (TMP-SMX) 5 mg/kg TMP and 25 mg/kg SMX PO or IV BID. TMP-SMX can be considered when the availability of other regimens is limited or when patients need IV therapy
- Atovaquone 1,500 mg PO BID + pyrimethamine + folinic acid (pyrimethamine and folinic acid as described above)
- Atovaquone 1,500 mg PO BID + sulfadiazine 1,000-1,500 mg PO Q6H (sulfadiazine dosing as above)
- Atovaquone 1,500 mg PO BID
- Pyrimethamine + leucovorin (dosing as above) + azithromycin 900-1,200 mg PO QD

Note: The regimens that contain sulfadiazine, TMP-SMX, or atovaquone also are effective in

preventing *Pneumocystis jiroveci* pneumonia (PCP), so patients on these regimens do not need additional PCP prophylaxis.

Adjunctive corticosteroids (e.g., dexamethasone 4 mg PO or IV Q6H) may be indicated for patients with CNS mass effect or edema. Use is based on clinical judgment and should be discontinued as soon as it is feasible to do so.

Anticonvulsant therapy should be given to patients with a history of seizures (but not to those who have not had seizures).

Ventilatory support may be necessary if severe CNS symptomatology is present.

Chronic Maintenance Therapy

After at least 6 weeks of initial therapy and significant clinical and radiologic improvement, chronic maintenance therapy can be considered.

Preferred

- Pyrimethamine 25-50 mg PO QD + sulfadiazine 2,000-4,000 mg PO daily in 2-4 divided doses + folinic acid 10-25 mg PO QD (also effective as PCP prophylaxis)

Alternative

- Pyrimethamine 25-50 mg PO QD + clindamycin 600 mg PO Q8H + folinic acid 10-25 mg PO QD
- TMP-SMX double-strength 1 tablet PO BID
- Atovaquone 750-1,500 mg PO BID + pyrimethamine 25-50 mg PO QD (+ folinic acid 10-25 mg PO QD)
- Atovaquone 750-1,500 mg PO BID + sulfadiazine 2,000-4,000 mg PO daily in 2-4 divided doses (also effective as PCP prophylaxis)
- Atovaquone 750-1,500 mg PO BID

For patients who complete acute therapy successfully, have resolution of signs and symptoms of toxoplasmosis, and have immune

reconstitution (with CD4 counts >200 cells/ μ L) for more than 6 months on ART, it is reasonable to consider discontinuing maintenance therapy. Some specialists would require resolution of CNS lesions on radiologic studies before discontinuation of therapy. Patients must be observed for recurrence of symptoms, and treatment should be restarted if the CD4 count decreases to <200 cells/ μ L.

Considerations During Pregnancy

All pregnant women should be tested for *T. gondii*. If the result is positive, evaluate the pregnant woman for signs or symptoms of toxoplasmosis and the neonate for evidence of congenital infection. Perinatal transmission usually occurs only with acute maternal infection, but in advanced HIV, it may occur with reactivation of chronic infection. If *T. gondii* infection occurs during pregnancy, consult with maternal-fetal and infectious disease specialists. Treatment for pregnant women is the same as for nonpregnant adults (see above). Note that sulfadiazine taken at the time of delivery may increase the risk of neonatal hyperbilirubinemia and kernicterus.

- Educate patients about the benefits of ART in strengthening the immune system and preventing opportunistic infections such as toxoplasmosis.
- Advise patients to contact the clinic promptly if symptoms worsen or if new symptoms develop.
- Toxoplasmosis is a late-stage HIV opportunistic infection that indicates profound immune suppression. Some patients may not respond to treatment or to ART. As with any patient who is at risk of a life-threatening HIV-related disease, clinicians should discuss advance directives and durable power of attorney with patients. Referral to a social worker, mental health clinician, or chaplain experienced in such issues may facilitate this discussion.

Patient Education

- Advise patients that antimicrobial therapy alone will not eradicate toxoplasmosis, but should decrease symptoms and improve quality of life. If medications are discontinued, the disease is likely to recur, unless the CD4 count increases to >100-200 cells/ μ L in response to ART.
- Inform patients that suppressive therapy must be continued to prevent recurrence. The duration of this therapy may be lifelong.
- It is essential for patients to take all medicines exactly as prescribed. If doses are missed, or if the medications are stopped and restarted, *Toxoplasma* can develop resistance to the medications. If patients are having trouble taking the medication on schedule, they should contact their health care provider immediately.



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