

# HIV AIDS Clinical Care: Common Complaints

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# 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

## Important Notice

The U.S. Department of Health and Human Services (HHS) HIV/AIDS Bureau is committed to providing accurate information on the care of HIV-infected persons. It is important to be aware that management options and protocols change over time. Forthcoming HHS guidance on certain topics may differ from recommendations contained in this *Guide*. Readers are encouraged to check for updates to treatment guidelines at AIDS Info ([aidsinfo.nih.gov](http://aidsinfo.nih.gov)) and for updates to drug information at Drugs@FDA ([www.accessdata.fda.gov/scripts/cder/drugsatfda](http://www.accessdata.fda.gov/scripts/cder/drugsatfda)).

# Diarrhea

## Background

Diarrhea is a common complaint among HIV-infected individuals, and has a variety of causes. Episodes may be acute and brief, intermittent or recurrent, or, in some cases, chronic and severe. If diarrhea persists, it may cause dehydration, poor nutrition, and weight loss. Diarrhea may diminish patients' quality of life significantly, and may interfere with adherence to and efficacy of antiretroviral (ARV) medications.

Diarrhea is defined in various ways, but commonly as more than 4 loose or watery stools per day for more than 3 days. Duration is classified as follows:

- Acute: <2 weeks
- Persistent: 2-4 weeks
- Chronic: >4 weeks

The causes of diarrhea, both infectious and noninfectious, found in HIV-infected individuals with normal or mildly depressed CD4 cell counts are likely to be similar to those in HIV-uninfected persons. Among the noninfectious causes of diarrhea, adverse effects of ARVs and other medications are particularly common. Persons with advanced immunodeficiency are more likely to have infections, including opportunistic infections, as the cause of diarrhea.

Infectious diarrhea typically involves either the small or the large intestine, and the patient's history often suggests the site of the problem. Infections of the small intestine (enteritis) commonly produce generalized or periumbilical abdominal cramps, large-volume diarrhea without blood, and frequently dehydration. Large-intestine infections (colitis) often produce lower abdominal pain, an unproductive urge to defecate, and frequent small-volume stools with blood and pus.

## S: Subjective

The patient complains of diarrhea. Take a thorough history, including the following:

- Onset of diarrhea: sudden or gradual
- Frequency (times per day, last episode)
- Stool consistency (soft vs. liquid)
- Stool color (gray, white, or greasy stools: possible cholelithiasis or pancreatitis; dark stools: possible gastrointestinal bleeding)
- Bloody stools (may indicate invasive organisms, inflammation, ischemia, or neoplasm)
- Rectal bleeding
- Straining at stool
- Pain with defecation, rectal discharge (consider sexually transmitted diseases, herpes simplex virus)
- Nausea or vomiting (within 6 hours of ingesting food, consider foodborne illness, gastroenteritis)
- Weight loss: quantify amount and time frame
- Abdominal pain or cramping; location if present
- Fever (consider invasive pathogens: *Shigella*, *Campylobacter*, *Salmonella*, *Clostridium difficile*)
- Other associated symptoms (e.g., bloating, flatus)

- Allergies (to foods or medications)
- Aggravating factors (e.g., dairy products, fatty or spicy foods)
- Alleviating factors (e.g., fasting)
- Treatments tried (e.g., over-the-counter antidiarrheals)
- Contact with others with similar symptoms
- Previous episodes of diarrhea
- History of cytomegalovirus (CMV), *Mycobacterium avium* complex (MAC), or other infections involving the gastrointestinal tract
- Family history of inflammatory bowel disease, celiac disease
- Oral-anal sexual contact (males and females)
- Receptive anal intercourse
- Exposure to unsafely prepared food (e.g., raw, undercooked, spoiled), unpasteurized milk or juices
- Exposure to possibly contaminated water (swimming in or drinking from well, lake, or stream) (consider parasites, including *Giardia*)
- Exposure to non-toilet-trained infants and children (e.g., at a daycare facility), pets, farm animals, reptiles (consider *Giardia*, *Salmonella*)
- Recent travel (enterotoxigenic *Escherichia coli*, *Shigella*, *Rotavirus*, *Salmonella*, *Campylobacter*, *Giardia*, *Entamoeba histolytica*)
- Antibiotic use or exposure in recent weeks or months or recent hospitalization (consider *C. difficile*)
- ARV medications, especially ritonavir-boosted protease inhibitors; check relationship of diarrhea onset to initiation of ARVs
- Other current and recent medications (prescribed or over-the-counter), including supplements and herbal preparations

- Dietary factors, especially “sugar-free” foods (containing nonabsorbable carbohydrates), fat substitutes, milk products, and shellfish, or heavy intake of fruits, fruit juices, or caffeine
- Alcohol and recreational drug use; withdrawal

## O: Objective

Record vital signs, including temperature, orthostatic heart rate, blood pressure measurements, and weight. Compare these with recent or baseline values. Perform a thorough physical examination, including evaluation of the following:

- Hydration status (skin turgor, mucous membrane moistness)
- Nutritional status (body habitus, muscle mass, skin and hair integrity)
- Oropharynx (lesions, candidiasis, ulcerations, Kaposi sarcoma)
- Optic fundi (signs of CMV infection)
- Abdomen (distention, bowel sounds, tenderness, organomegaly, masses, adenopathy)
- Rectum (masses, tenderness, bloody stool)

Review recent CD4 cell counts. Low CD4 counts increase the risk of chronic or systemic illnesses and opportunistic infections.

## A: Assessment

The differential diagnosis of diarrhea is broad and includes the following infectious and noninfectious causes. The CD4 cell count is important in stratifying risk of infection with opportunistic pathogens; some organisms cause disease only with severe immunosuppression.

## Infectious Causes

Table 1. Infectious Causes

Severity	Differential Diagnosis
<b>Active diarrhea, any CD4 count</b>	<ul style="list-style-type: none"> <li>• Viruses (especially Norwalk virus)</li> <li>• Viral hepatitis</li> <li>• Herpes enteritis</li> <li>• <i>C. difficile</i> (suspect in patients who have recently undergone treatment with antibiotics, or hospitalization)</li> <li>• <i>Salmonella</i></li> <li>• <i>Shigella</i></li> <li>• <i>Campylobacter</i></li> <li>• <i>E. coli</i> O157:H7</li> </ul>
<b>Chronic diarrhea, any CD4 count</b>	<ul style="list-style-type: none"> <li>• <i>C. difficile</i> (suspect in patients who have been treated with antibiotics)</li> <li>• <i>Giardia lamblia</i></li> <li>• <i>E. histolytica</i></li> </ul>
<b>Chronic diarrhea, CD4 count &lt;300 cells/μL</b>	<ul style="list-style-type: none"> <li>• Microsporidia</li> <li>• <i>Cryptosporidium parvum</i></li> <li>• MAC (CD4 count &lt;50 cells/μL)</li> <li>• <i>Isospora belli</i></li> <li>• CMV (CD4 count &lt;50 cells/μL)</li> </ul>

Adapted from: *Infectious Causes of Diarrhea in Patients with HIV*, Table 8-8. In: Bartlett JG, Cheever LW, Johnson MP, et al., eds. *A Guide to Primary Care of People with HIV/AIDS*. Rockville, MD: U.S. Department of Health and Human Services, Health Resources and Services Administration; 2004. Available at [hab.hrsa.gov/deliverhivaidscafe/files/primary2004ed.pdf](http://hab.hrsa.gov/deliverhivaidscafe/files/primary2004ed.pdf). Accessed December 1, 2013.

## Noninfectious Causes

- Medication adverse effects, common with many medications including some ARVs:
  - Protease inhibitors (especially ritonavir and nelfinavir)
  - Didanosine buffered tablets (no longer available in the United States)
  - Cobicistat (present in Stribild)
- Irritable bowel syndrome
- Inflammatory bowel disease (ulcerative colitis, Crohn disease)
- Lymphoma
- Lactose intolerance
- Celiac disease
- Small intestinal bacterial overgrowth
- Pancreatic insufficiency
- Diverticulitis
- Fecal incontinence
- Laxative abuse

## P: Plan

### Diagnostic Evaluation

For suspected infections, perform laboratory studies including complete blood count with differential, serum electrolyte panel, and liver function tests. Check stool for white blood cells and blood. Perform stool studies as indicated by the patient's presentation (bacterial culture, ova and parasites, microsporidia, cryptosporidia, *Giardia* antigen, *C. difficile* toxin assay). Order additional studies as suggested by the history (e.g., blood cultures, MAC cultures, hepatitis serologies, retinal examination for CMV). If noninfectious causes are suspected, perform evaluation for these etiologies as indicated (e.g., fecal fat concentration [for steatorrhea], stool osmolar gap [for osmotic diarrhea], anti-tissue transglutaminase [TTG] antibody [for celiac disease], or D-xylose [for pancreatic insufficiency]).

If the patient is febrile, perform a complete fever workup as appropriate (see chapter *Fever*).

Check the CD4 cell count and HIV viral load, if not checked recently.

If stool study results are negative (ova and parasite negative in three successive samples) and the patient has severe symptoms, particularly in the case of advanced immunodeficiency, refer to a gastroenterologist for colonoscopy or flexible sigmoidoscopy with biopsy. Endoscopy with biopsy is the best procedure for identifying certain conditions, including CMV colitis and inflammatory bowel disease. If all study results are negative but the diarrhea persists, consider repeat endoscopy in 6-8 weeks regardless of the level of immunodeficiency. Pathogens may be difficult to identify.

### Treatment

Once a diagnosis is made, initiate appropriate treatment. For seriously ill patients, presumptive treatment may be started while diagnostic tests are pending. If the cause of the diarrhea cannot be identified, consult with an HIV expert or a gastroenterologist.

- For moderate to severe acute diarrhea, including dysentery (bloody diarrhea), empiric treatment can be given pending stool study results or in settings with limited resources for workup. If bacterial pathogens are suspected, use oral fluoroquinolones (e.g., ciprofloxacin 500 mg BID or levofloxacin 500 mg QD) for 5 days. Monitor effectiveness and adjust therapy according to the results of diagnostic studies and clinical response. Specific treatment with antimicrobials is guided by the pathogens identified in stool studies or on biopsy.

- For suspected small intestinal bacterial overgrowth consider treatment with an appropriate antimicrobial (e.g., rifaximin 1,200-1,600 mg per day for 7-10 days).
- For mild persistent diarrhea with no identified pathogen, treat with an antidiarrheal agent (see below). For patients whose diarrhea is suspected to be caused by ARV agents or other medications, symptomatic treatment also may be tried. Diarrhea owing to protease inhibitors often decreases after a few weeks without treatment. For persistent, daily ARV-associated diarrhea, antidiarrheal agents may be given on a scheduled basis (rather than as needed). If the diarrhea cannot be controlled, a change in ARV regimen should be considered.

### Symptomatic treatments

- Antimotility agents such as loperamide (Imodium) in over-the-counter or prescription strengths and atropine/diphenoxylate (Lomotil) are useful for many patients. The suggested dosage is 2 tablets after each loose bowel movement, not to exceed 8 tablets per day. These agents should not be used if patients have bloody diarrhea or if the presence of *C. difficile* is suspected.
- Pharmacologic-nutritional approaches include the use of calcium supplementation (500 mg BID or TID). Patients with diarrhea related to protease inhibitors may find that taking calcium with each dose of protease inhibitors can decrease or prevent diarrhea. Note that magnesium supplements may worsen diarrhea.

- Pancrelipase can be useful in managing chronic diarrhea caused by malabsorption. It comes in different formulations with differing amounts of pancreatic enzymes; usual dosage is 2-3 capsules TID with meals, titrated downward according to response.
- Cholestyramine or psyllium (e.g., Metamucil) may reduce diarrhea by slowing peristalsis and adding bulk to stools. Avoid administering cholestyramine with other medications because it may impair their absorption.
- Crofelemer, an antisecretory antidiarrheal agent, is approved by the U.S. Food and Drug Administration for treatment of noninfectious diarrhea in HIV-infected adults on antiretroviral therapy (ART). The dosage is 135 mg BID. Infectious causes should be ruled out before treatment with crofelemer.
- A combination of these treatments may be needed to control chronic diarrhea, and they can be continued for patients after an infectious process has been ruled out.

### Nutrition and hydration

Encourage frequent intake of soft, easily digested foods such as bananas, rice, wheat, potatoes, noodles, boiled vegetables, crackers, and soups. Encourage hydration with fruit drinks, tea, “flat” carbonated beverages, and water. Patients should avoid high-sugar drinks, caffeinated beverages, alcohol, high-fiber foods, greasy or spicy foods, and dairy products. Many patients may benefit from a trial of a lactose-free, low-fiber, or low-fat diet. Patients should use nutritional supplements as needed or as recommended by a dietitian. In case of chronic or severe diarrhea, or significant weight loss, refer to a dietitian for further recommendations.

Patients with severe diarrhea must maintain adequate hydration, by mouth if possible. In severe cases, IV administration of fluids may be necessary. Oral rehydration solutions

include the World Health Organization formula, Pedialyte, Rehydralyte, Rice-Lyte, and Resol. Homemade alternatives include the following:

- Combine 1/2 teaspoon of salt, 1 teaspoon of baking soda, 8 teaspoons of sugar, and 8 ounces of orange juice; add water to make 1 liter and drink.
- Drink 1 glass containing 8 ounces of apple, orange, or other juice; 1/2 teaspoon of corn syrup or honey; and a pinch of salt; then drink 1 glass containing 8 ounces of water and 1/4 teaspoon of baking soda.
- Mix 1/2 cup of dry, precooked baby rice cereal with 2 cups of water (boil first in areas with poor water quality); add 1/4 teaspoon of salt and drink.

### Patient Education

- Diarrhea can have many causes. Instruct patients to notify their health care provider if they develop new or worsening symptoms.
- Instruct patients to take their medications exactly as directed and to call their health care provider if they experience worsening diarrhea or other symptoms such as fever, nausea, vomiting, or pain.
- Patients must stay nourished and well hydrated even if they are having diarrhea. Instruct patients to eat small, frequent meals and to avoid dairy products, greasy food, and high-fat meals.
- Instruct patients to maintain good handwashing practices during diarrheal illnesses to prevent infection in close contacts or household members.
- Some diarrheal illnesses are reportable; advise patients that they may be contacted by the local health department.

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# Ear, Nose, Sinus, Mouth

## Background

HIV-infected individuals frequently experience infections and neoplasms that affect the ears, nose, sinuses, and mouth. The degree of immunosuppression, as reflected by a patient's CD4 cell count, can affect the severity, likelihood of recurrence, and response to therapy for various infections and neoplasms.

Patients may present with ear, nose, sinus, or mouth complaints early in the course of HIV infection, perhaps even before they are aware of their infection. Some conditions arise more commonly in patients with advanced HIV infection. Certain conditions (e.g., oral candidiasis) should prompt consideration of HIV testing in patients without known infection.

## Ears

HIV-infected patients may experience recurrent acute otitis media and serous otitis media. Nasopharyngeal lymphoid hyperplasia, sinusitis, or allergies may contribute to dysfunction of the eustachian tubes. Unilateral and bilateral sensorineural hearing loss has been reported and may be caused by HIV infection involving the central nervous system (CNS) or the auditory nerve. Hearing loss also may be caused by syphilis, other CNS infections, chronic otitis media, neoplasms, and certain medications (including nucleoside analogues in rare cases). The pathophysiology, causative organisms, and incidence of external-ear infections appear to be the same in HIV-infected patients as in HIV-uninfected individuals.

## S: Subjective

The patient may complain of ear pain, decreased hearing or hearing loss, a feeling of fullness in the ear, vertigo, or a popping or snapping sensation in the ear.

Obtain information regarding the following during the history:

- Medications (prescription and over-the-counter) and herbal supplements, current and past
- Current or recent sinus infection
- Associated symptoms
- Drainage or blood from the ear
- Head or ear trauma

## O: Objective

CD4 count is an important measure of immunosuppression and a recent CD4 count is important in determining whether the patient is at risk of opportunistic infections as causes of ear complaints.

Perform visual and otoscopic inspection, including evaluation for skin abnormalities, lesions, cerumen impaction or foreign body, lymphadenopathy, and adenotonsillar hypertrophy.

If hearing loss is reported or suspected, evaluate hearing and refer the patient for an audiogram. Perform a neurologic examination and test for syphilis (e.g., rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL] test) and other possible causes.

## A/P: Assessment and Plan

### Otitis Externa/Interna

Proceed as with an immunocompetent patient. A chronic or atypical presentation in an HIV-infected patient warrants a thorough evaluation, including cultures, biopsy, radiographic scans, and referral to an ear, nose, and throat (ENT) specialist.

### Hearing Loss

A patient with hearing loss should be referred for evaluation or treated, depending on the cause. Avoid ototoxic medications (e.g., furosemide, aminoglycosides).

## Nose and Sinuses

Nasal and paranasal sinus conditions occur frequently in HIV-infected patients. Sinusitis, nasal obstruction, allergic rhinitis, and nasal lesions are common. Epistaxis can occur in patients with platelet disorders (e.g., idiopathic thrombocytopenic purpura [ITP]).

## S: Subjective

The patient may complain of “stuffy nose,” rhinorrhea, epistaxis, frontal or maxillary headaches (worse at night or early morning), pain in the nostrils, persistent postnasal drip, mucopurulent nasal discharge, general malaise, aching or pressure behind the eyes, or toothache-like pain.

Obtain information regarding the following during the history:

- Medications (prescription and over-the-counter) and herbal supplements, current and past
- Current or recent sinus infection
- Previous sinus surgery
- Recent or current upper respiratory infection (URI)
- Nasal bleeding or discharge
- Facial trauma
- Allergic rhinitis
- Positional pain; worse when patient bends forward?
- Tobacco use
- Fever
- Headache
- Mucopurulent nasal drainage

## O: Objective

CD4 count is an important measure of immunosuppression and a recent CD4 count is a key element in determining whether the patient is at risk of opportunistic infections as causes of nasal and sinus complaints.

Examine the nose and sinuses. Check the nasal mucosa with a light and a speculum, looking for areas of bleeding, purulent drainage, ulcerated lesions, or discolored areas. Palpate or percuss the sinuses for areas of tenderness, look for areas of swelling over the sinuses, and visualize the posterior pharynx for mucopurulent drainage. Transillumination may be helpful. Examine the teeth and gums for caries and inflammation of the gingivae. Check maxillary teeth with the use of a tongue blade (5-10% of maxillary sinusitis is attributable to dental root infection). Refer to a dentist for tooth sensitivity or caries.

## A: Assessment

- Possible causes of epistaxis include coagulopathy, ITP, lesions of herpes simplex virus (HSV), and Kaposi sarcoma (KS) or other tumors. Suspect ITP if the platelet count is low and bleeding is difficult to control.
- Acute infection of one or more of the paranasal sinuses is common. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are seen in both HIV-uninfected and HIV-infected patients, whereas *Staphylococcus aureus* and *Pseudomonas aeruginosa* are found more often in HIV-infected patients. Fungi may be the causative agents, especially in patients with severe immunosuppression.
- Chronic sinusitis occurs frequently in patients with HIV infection and may be polymicrobial or anaerobic. In patients with low CD4 cell counts, fungal sinusitis may occur.
- Nasal obstruction may be caused by adenoidal hypertrophy, chronic sinusitis, allergic rhinitis, or neoplasm.
- Tumors may be caused by KS, squamous papilloma, or lymphoma; biopsy is necessary for determining the cause.
- Painful, ulcerated vesicles in the nasal mucosa may be caused by HSV or other infections.

## P: Plan

### Acute Sinusitis

Combination therapy with antibiotics, decongestants, mucolytics, saline nasal spray, and topical nasal steroids may be effective. See chapter *Sinusitis* for details. Note: For patients taking antiretroviral (ARV) regimens that include ritonavir or cobicistat, fluticasone (Flonase) nasal spray should not be used, and budesonide (Rhinocort Aqua) should be avoided if possible; see “Potential ARV Interactions,” below.

### Chronic Sinusitis

Treat with a systemic decongestant (e.g., guaifenesin) or a saline nasal spray BID. Patients with exacerbations of sinusitis should be treated as for acute sinusitis. For more detailed information, see chapter *Sinusitis*. With patients taking ritonavir-boosted PIs, avoid fluticasone and budesonide nasal sprays; see “Potential ARV Interactions,” below.

### Allergic Rhinitis

Patients should avoid exposure to known or suspected allergens. Nasal steroids may be very effective, but avoid fluticasone and budesonide nasal sprays with patients taking ritonavir or cobicistat (see “Potential ARV Interactions,” below). Second-generation nonsedating antihistamines such as cetirizine, fexofenadine, and loratadine are not as effective as nasal steroids, but may give additional symptom relief. Note that ritonavir may increase the serum levels and half-life of cetirizine. Daily nasal lavage with normal saline often is beneficial.

### Nasal Obstruction

Perform magnetic resonance imaging (MRI) or computed tomography (CT) scan with biopsy for mass lesions or asymmetric nasal lymphoid tissue. Refer to an ENT specialist.

### Epistaxis

Epistaxis caused by coagulopathy or tumor is managed the same as for immunocompetent patients with these conditions. Cauterization of an identified bleeding point or packing may be necessary. ITP should be managed in collaboration with a hematologist; antiretroviral therapy (ART) typically is used for chronic management, and corticosteroids or other therapies may be used for acute management.

### Potential ARV Interactions

**Caution:** Protease inhibitors (PIs), particularly ritonavir-boosted PIs, and cobicistat [e.g., in coformulated elvitegravir/cobicistat/tenofovir/emtricitabine (Stribild)] may increase serum glucocorticoid levels if used concurrently with nasal steroids. Fluticasone (Flonase) nasal spray should not be used with ritonavir-boosted PIs or cobicistat unless expected benefits outweigh possible risks, and should be avoided, if possible, in patients taking unboosted PIs. Budesonide (Rhinocort Aqua) nasal spray should be avoided with ritonavir-boosted PIs and cobicistat. Interactions of PIs and cobicistat with other nasal steroids have not been well studied.

Ritonavir and cobicistat may increase serum levels of cetirizine and may prolong its half-life; start with low dosage and monitor for adverse effects.

## Mouth and Throat

The oral cavity is one of the most common areas of symptoms in patients with HIV infection. Conditions that arise in the oral cavity may result from infectious, benign inflammatory, neoplastic, or degenerative processes.

### S: Subjective

The patient may complain of white patches and red areas on the dorsal surface of the tongue and the palate, decreased taste sensation, white lesions along the lateral margins of the tongue, ulcers, nonhealing lesions at the corners of the mouth, sore gums, loose teeth, dysphagia, orodynophagia.

Obtain information regarding the following during the history:

- Medications (prescription and over-the-counter) and herbal supplements (note that some medications may cause aphthous ulcers)
- Usual oral hygiene (toothbrushing, tongue brushing or scraping, flossing, use of mouthwash)
- Date of last dental examination
- Use of tobacco (cigarettes, chewing tobacco)
- Involuntary weight loss

### O: Objective

Because the CD4 count reflects degree of immunosuppression, a recent CD4 count is helpful in determining whether the patient is at risk of opportunistic infections as causes of oral complaints.

Thorough examination of the mouth and throat with a tongue depressor and a good light is mandatory. Observe for white patches or plaques on the mucous membranes that can be partially removed by scraping with a tongue blade (candidiasis). Examine the dorsal surface of the tongue and hard and soft palates for red, flat, subtle lesions (erythematous candidiasis). Look for ribbed, whitish lesions on the lateral aspects of the tongue that cannot be scraped off (oral hairy leukoplakia). Check for ulcerations, inflamed gums, and loose teeth (see section *Oral Health*). Look for discoloration or nodular lesions on the hard palate (Kaposi sarcoma). Check the pharynx for adenotonsillar hypertrophy. Rule out HIV-unrelated causes of pharyngitis, including streptococci or respiratory viruses.

## A/P: Assessment and Plan

Perform biopsy, culture, and potassium hydroxide (KOH) preparation of lesions as indicated.

### Oral Candidiasis (Thrush)

Oral candidiasis is most likely to occur when the CD4 count is  $<200$  cells/ $\mu$ L, but it can occur at any CD4 level and in HIV-uninfected individuals. It may appear as creamy white plaques on the tongue or buccal mucosa or as erythematous lesions on the dorsal surface of the tongue or the palate. The most common treatment strategy is empiric therapy with topical or systemic antifungal agents. For more details, see chapter *Candidiasis, Oral and Esophageal*.

### Angular Cheilitis

Angular cheilitis is also caused by *Candida* species, and it is characterized by fissuring at the corners of the mouth. For information on treatment, see chapter *Candidiasis, Oral and Esophageal*.

### Oral Hairy Leukoplakia

Oral hairy leukoplakia (OHL) is caused by Epstein-Barr virus and appears as raised, ribbed, “hairy” white lesions along the lateral margins of the tongue. Lesions are primarily asymptomatic, and treatment generally is not needed. Lesions often resolve with effective ART. For more details, see chapter *Oral Hairy Leukoplakia*.

### Kaposi Sarcoma

KS appears as red, blue, or purplish lesions that are flat or nodular, and solitary or multiple. Lesions appear most commonly on the hard palate but also occur on the gingival surfaces and elsewhere in the mouth. A definitive diagnosis requires biopsy and histologic examination. KS often resolves with ART and successful immune reconstitution. If lesions do not respond to ART or if they are severe or numerous, refer to an oncology specialist for chemotherapy. For more details, see chapter *Kaposi Sarcoma*.

### Gingivitis

See chapter *Necrotizing Ulcerative Periodontitis and Gingivitis* for details.

### Herpes Simplex Virus

HSV lesions occur on the palate, gingivae, or other mucosal surfaces. They appear as single or clustered vesicles and may extend onto adjacent skin of the lips and face to form a large herpetic lesion. Lesions tend to be more common, persist longer, recur more often, and be larger and more numerous in HIV-infected patients, especially those with significant immunosuppression, than in healthy individuals. Empiric treatment with valacyclovir, famciclovir, or acyclovir is appropriate. For more details, see chapter *Herpes Simplex, Mucocutaneous*.

### Aphthous Ulcers

Aphthous ulcers are eroded, well-defined lesions surrounded by erythema, ranging in size from  $<6$  mm to several centimeters in diameter. The ulcers can appear anywhere in the oral cavity or pharynx and may be recurrent; they are extremely painful. Treatment may involve topical steroids or other methods. For more details, see chapter *Oral Ulceration*.

### Oral Warts (Human Papillomavirus)

Oral warts may appear as solitary or multiple nodules. The lesions may be smooth, raised masses resembling focal epithelial hyperplasia, or small papuliferous or cauliflower-like projections. See chapter *Oral Warts*.

### *Neisseria gonorrhoeae* Pharyngitis

*Neisseria gonorrhoeae* may be transmitted by orogenital exposure; the patient may have mild symptoms (e.g., sore throat) or be asymptomatic. Physical examination may reveal an erythematous pharynx or exudates. Anterior cervical lymphadenopathy also may be present. Most cases of *N. gonorrhoeae* pharyngeal infection will resolve spontaneously without treatment and usually do not cause adverse sequelae. However, treatment should be initiated to reduce the spread of the infection (see chapter *Gonorrhea and Chlamydia*). Regular screening is recommended for patients at risk of *N. gonorrhoeae* infection.

### Medication-Related Causes of Mouth or Throat Lesions

- Candidiasis: antibiotics
- Xerostomia: antihistamines, anticholinergics, tricyclics, antipsychotic
- Gingival hyperplasia: phenytoin, calcium channel blockers

### Other Conditions

Most of the above complications also can occur in the esophagus. See chapters *Esophageal Problems*; *Candidiasis, Oral and Esophageal*; and *Cytomegalovirus Disease*.

If patient is having mouth pain, anorexia, or problems with taste, treat the condition appropriately and refer to an HIV-experienced dentist for evaluation and further treatment as needed. Refer to a dietitian for assistance with dietary needs (e.g., nutritional supplements).

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# Esophageal Problems

## Background

Esophageal problems in HIV-infected patients include difficulty swallowing (dysphagia) or midline retrosternal pain when swallowing (odynophagia). Pain may be diffuse throughout the esophagus or localized in specific areas.

Several conditions may cause esophageal problems. Of the infectious causes of dysphagia in HIV-infected patients, *Candida* is the most common (50-70%). Drug-induced dysphagia, gastroesophageal reflux disease (GERD), vomiting, and hiatal hernia also can cause esophagitis. Less commonly, esophageal cancer or another cause of stricture may produce symptoms. Neuromuscular or neurological causes may be seen in patients with advanced AIDS.

If untreated, esophageal problems may result in esophageal ulcers, scarring of the esophagus, dehydration, and weight loss.

## S: Subjective

The patient may complain of difficulty swallowing, a feeling of something being “stuck in the throat,” retrosternal pain when eating, “hiccups,” indigestion (“heartburn”), retrosternal burning, acid reflux, nausea, vomiting, or abdominal pain. Ascertain the following during the history:

- Medications (prescription and over-the-counter) and herbal supplements, current and past
- Concurrent gastrointestinal (GI) symptoms, such as abdominal pain or diarrhea
- Recent dietary history
- Location and characteristics of pain (diffuse or focal)
- Oral thrush
- Aphthous ulcers
- Cytomegalovirus (CMV)
- *Candida* esophagitis
- Gastroesophageal reflux disease (GERD)
- Hiatal hernia
- Presence of dysphagia to solids, liquids, or both
- Hematemesis or melena

## O: Objective

Include the following in the physical examination:

- Measure vital signs (temperature may be elevated with certain infections, such as CMV, but not with herpes simplex virus [HSV], candidiasis, or idiopathic ulcers).
- Record weight (and compare with previous weights).
- Assess for oral candidiasis, lesions, and masses.
- Examine optic fundi to evaluate for CMV retinitis (in patients with CD4 counts of <50-100 cells/ $\mu$ L).
- Palpate for thyroid enlargement.
- Palpate the neck and supraclavicular and infraclavicular areas for lymphadenopathy.
- Assess the abdomen for masses, tenderness, and organomegaly.
- Perform a rectal examination to obtain stool for occult blood.
- Perform a neurologic examination.
- Check the CD4 cell count and HIV viral load to determine the level of immunosuppression and assess the risk of opportunistic infections as causes of esophageal complaints.

## A: Assessment

Common causes of esophageal problems are as follows:

- Candidiasis (common with a CD4 count of <200 cells/ $\mu$ L or recent exposure to steroids or antibiotics)
- Most medications, including antiretroviral agents, can cause nausea and GI-related symptoms; the following medications are commonly associated with difficulty swallowing or heartburn: aspirin, nonsteroidal antiinflammatory drugs, potassium chloride, iron, tetracycline, theophylline, anticholinergic agents, calcium channel blockers, meperidine, and progesterone tablets
- Foods can irritate the esophagus, including citrus fruits, mints, coffee, chocolate, and spicy foods
- GERD

Less-common causes of esophageal problems include:

- CMV, HSV, idiopathic or aphthous ulcers
- Kaposi sarcoma, lymphoma, tuberculosis, *Mycobacterium avium* complex (MAC), histoplasmosis
- Cardiac chest pain

## P: Plan

### Diagnostic Evaluation

Diagnosis often can be made on clinical grounds; in this case, empiric treatment may be initiated (see below). If the diagnosis is unclear, consider endoscopy or radiographic imaging (e.g., computed tomography or barium swallow).

If the patient has dysphagia, odynophagia, unexplained weight loss, GI bleeding, anemia, or atypical symptoms, refer promptly for GI evaluation and endoscopy, or other evaluation as suggested by symptoms.

## Treatment

Determine whether the patient is able to swallow pills before giving oral medications. If pills are not tolerated, the patient may need liquids or troches.

For patients with severe oral or esophageal pain, viscous lidocaine 1% 5-10 mL 2-4 times daily (with swallowing precautions) or Magic Mouthwash (viscous lidocaine 1%, tetracycline, diphenhydramine, and nystatin compounded 1:1:1:1) may be tried.

Other treatments may depend on the underlying cause:

- **Esophageal candidiasis:** Fluconazole is the drug of choice. If symptoms resolve within 7-10 days, no further testing is required. See chapter *Candidiasis, Oral and Esophageal* for more treatment options and for dosing information.
- **Medication related:** Remove the offending drug(s), and institute a trial of H2 blockers or proton pump inhibitors (PPIs) as appropriate (caution: see “Potential ARV Interactions,” below).
- **Food related:** Modify the diet and institute a trial of H2 blockers or PPIs as appropriate (caution: see “Potential ARV Interactions,” below).
- **“Heartburn” or GERD:** Patients whose primary symptoms are more typical of “heartburn” or reflux, especially those with a history of GERD, should receive a trial of H2 blockers or a PPI as appropriate (these may decrease absorption of atazanavir and rilpivirine; see “Potential ARV Interactions,” below). Reevaluate after 2-4 weeks; if symptoms are controlled, treat for 4-8 weeks, then reduce the dosage to the lowest effective amount.

Patients may require maintenance therapy for an indefinite period because of the high likelihood of recurrence. If symptoms do not respond to full-dose acid-blocking therapy, refer for GI evaluation.



- **GERD:** For nonpharmacologic treatment, in cases of obesity, counsel patients to lose weight, stop smoking, elevate the head of the bed, eat smaller meals, avoid eating food 2-3 hours before bedtime, and reduce fat in the diet to  $\leq 30\%$  of calorie consumption.
- **CMV:** Treat with anti-CMV medications (e.g., oral valganciclovir). See chapter *Cytomegalovirus Disease* for details.
- **HSV:** Treat with antiviral medications, including acyclovir, famciclovir, and valacyclovir. See chapter *Herpes Simplex, Mucocutaneous*.
- **Aphthous ulcers:** These may respond to oral corticosteroids (consult with a specialist before this is undertaken). Alternatively, a combination of H2 blockers and sucralfate may be effective. In some circumstances, thalidomide 200 mg Q24H may be used. (**Note:** Thalidomide is teratogenic, and women of childbearing potential are not candidates for this therapy unless the potential benefits clearly outweigh the risks and appropriate prevention of pregnancy is undertaken.) Up to 40-50% of patients with aphthous ulcers experience relapse and require repeat treatment.
- **Neoplastic disease:** Treating this condition requires referral to an oncologist.

Esophageal conditions that do not resolve with treatment require referral to a GI specialist for diagnostic endoscopy, with biopsy and brushing for histopathology and cultures as appropriate.

## Diet

It is important that patients maintain adequate caloric intake, preferably with foods and liquids that can be swallowed easily. Nutritional supplements along with soft, bland, high-protein foods are recommended. Refer to a nutritionist as needed.

### Potential ARV Interactions

**Caution:** H2 blockers and PPIs interfere with the absorption of atazanavir and rilpivirine. For atazanavir, specific dosing strategies are required, and some combinations are contraindicated. For rilpivirine, PPIs are contraindicated and H2 blockers require specific dose timing. Polyvalent cations (e.g., magnesium, calcium, iron) contained in antacids, supplements, and other medications may lower serum levels of integrase inhibitors and require separate administration. See package inserts for dosage recommendations.

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# Eye Problems

## Background

The immunosuppression caused by HIV infection increases the incidence of eye infections. However, the risk of serious eye problems associated with advanced immunosuppression, such as blindness caused by cytomegalovirus (CMV) retinitis, is much lower in patients treated with effective antiretroviral therapy (ART). Common problems not unique to HIV-infected patients include dry eye, blepharitis, keratitis, and presbyopia. Infections that may affect the eye include herpes simplex virus (HSV), herpes zoster virus (HZV), and syphilis. More severely immunocompromised patients (CD4 count  $<100$  cells/ $\mu$ L) may experience CMV retinitis, Toxoplasma retinochoroiditis, cryptococcal chorioretinitis, and other conditions. Retinal detachment can result. Kaposi sarcoma (KS) also can affect the eye.

Immune reconstitution inflammatory syndrome (IRIS) may affect the eye in patients with advanced HIV disease soon after the initiation of effective ART. IRIS may lead to exacerbation of a previously treated opportunistic infection or a new presentation (often with unusual manifestations) of a previously subclinical infection. In the case of CMV, IRIS may present as retinitis, or less commonly as uveitis or vitreitis. IRIS retinitis typically occurs in patients whose CD4 counts have increased from  $<50$  cells/ $\mu$ L to 50-100 cells/ $\mu$ L while receiving ART.

Drug-induced ocular toxicity can be caused by many medications, including rifabutin, ethambutol, and cidofovir, and less often by high-dose didanosine (ddI, Videx), IV ganciclovir, IV acyclovir, and atovaquone.

## S: Subjective

The patient complains of dry eyes, blurred vision, floaters, sharp pains, flashing lights, central vision loss (“black holes”), vision field defects (“can only see half the page”), or peripheral vision loss (“looks like I’m in a tunnel”).

Ascertain the following during the history:

- Pain: clarify type and characteristics
- Unilateral or bilateral problem
- Visual defects (central or peripheral vision loss or distortion), scotomata (an area of lost or depressed vision surrounded by an area of less-depressed or normal vision); occurs with reading, distance, or both?
- Time course of symptoms
- Fever
- Headache
- Previous eye or vision problems

- Medications (prescription and over-the-counter) and herbal supplements, current and past
- Use of corrective lenses
- Date of last eye examination
- Recent or current varicella-zoster virus (VZV) or HSV infection

## O: Objective

Evaluate recent CD4 cell count and HIV viral load to determine whether the patient is at risk of opportunistic infections as causes of eye complaints. Also, do the following:

- Consider the patient’s age.
- Check vital signs, including blood pressure and temperature.
- Administer a visual acuity examination using the Snellen chart. Test the patient’s ability to read small print, such as classified ads.

- Consider using an Amsler grid to locate areas of retinal pathology.
- Examine the eyelids for lesions, inflammation, and swelling.
- Examine the external eye for edema, ptosis, conjunctival injection, and corneal clarity.
- Test cranial nerves II, III, IV, and VI.
- Perform funduscopic examination with pupillary dilatation, if available. Note retinal appearance, lesions, and condition of the disc, vessels, and macula.
- Examine the temples and scalp for tenderness.

### A/P: Assessment and Plan

Refer to an HIV-experienced ophthalmologist for dilated retinal or slit-lamp examination and definitive diagnosis. If symptoms raise suspicion of serious or vision-threatening conditions such as herpes ophthalmicus, CMV retinitis, or retinal necrosis, ophthalmologic evaluation should occur within 24-72 hours. Note that patients with HSV or VZV lesions in the V1 distribution (including the forehead, eyelids, or nose) should receive urgent ophthalmologic evaluation.

The differential diagnosis includes the following conditions:

#### Dry Eye (Keratoconjunctivitis Sicca)

The patient may complain of intermittent eye pain, intermittent blurred vision that clears with blinking, and mild eye irritation. The condition worsens with extended reading or computer use. Keratoconjunctivitis sicca is related to HIV-mediated inflammation with damage to the lacrimal glands. It occurs in 10-20% of HIV-infected patients, most often in those with advanced HIV disease. In patients with a CD4 count of >400 cells/ $\mu$ L and no other signs or symptoms, confirm that results of a recent eye examination were normal or refer for same, prescribe artificial tears, and monitor.

### Blepharitis

Blepharitis is inflammation of the eyelids, a common condition with dry eyes. The patient may complain of discharge and erythema of the eyes or eyelids. Of the bacterial causes, *Staphylococcus aureus* is the most common. Treatment includes cleaning of the eyelashes with warm water and mild shampoo, and applying antibiotic ointment if indicated.

### Infectious Keratitis

The patient may complain of photophobia, eye pain, decreased vision, and irritation. Infectious keratitis may be caused by VZV, HSV, CMV, bacteria, fungi, or *Microsporidia*. VZV and HSV are the most common infectious causes of keratitis in HIV-infected patients. Bacterial and fungal keratitis occur with equal frequency in HIV-infected and HIV-uninfected persons. Fungal infections are caused most often by *Candida* species, especially in intravenous drug users. Keratitis may be more severe and may recur more frequently in HIV-infected patients than in HIV-uninfected persons. Evaluation should include slit-lamp examination by an ophthalmologist.

### Refraction Problems

The patient may complain of blurring vision with near or distance vision. Other findings include an abnormal Snellen test or inability to read fine print. The condition may be attributable to presbyopia or other causes. Refer for ophthalmologic examination.

### Iridocyclitis/Anterior Uveitis

The patient may complain of redness or watering of the eyes, constriction of the pupil, and blurred vision. Anterior-chamber inflammation is fairly common among patients with HIV infection and is often associated with CMV or HSV retinitis. Ocular bacterial infections, syphilis, toxoplasmosis, and tuberculosis can cause severe symptoms. Fungal retinitis rarely causes iridocyclitis. Other causes include other systemic conditions

(e.g., reactive arthritis, sarcoidosis) and drug toxicity (e.g., rifabutin, cidofovir, ethambutol). Evaluation should include slit-lamp examination by an ophthalmologist.

Treatment should be directed at the causative pathogen or illness. If drug toxicity is suspected, the offending drug should be discontinued or reduced in dosage, if possible. Topical steroids may be indicated as an adjunctive measure. CMV IRIS may present as posterior uveitis; for suspected IRIS, consult an HIV-experienced ophthalmologist.

### HIV Retinopathy

The patient typically has no symptoms, but may complain of blurred vision, visual field defects, floaters, or flashing lights. Cotton wool spots on the retina appear as small fluffy white lesions with indistinct borders and without exudates or hemorrhages. Usually, these findings are benign and do not progress. Refer for ophthalmologic examination to rule out other causes.

### CMV Retinitis

Patients with retinitis caused by CMV infection may be asymptomatic or may experience blurred vision, floaters, scotomata, or central or peripheral vision loss or distortion. Retinal examination shows creamy to yellowish lesions, white granular areas with perivascular exudates, and hemorrhages (“cottage cheese and ketchup”). The abnormalities initially appear in the periphery, but progress if untreated to involve the macula and optic disc. CMV is a common complication of advanced HIV infection in patients with CD4 counts of <50 cells/ $\mu$ L. Vision loss usually is permanent. Urgent ophthalmology consultation and initiation of anti-CMV therapy are required. See chapter *Cytomegalovirus Disease*.

### Acute Retinal Necrosis

The patient may complain of eye pain, decreased visual acuity, and floaters. Rapidly progressing peripheral necrosis frequently causes blindness. Retinal necrosis usually is caused by VZV, although HSV and CMV also have been implicated. Treatment should be initiated urgently.

### *Toxoplasma* Retinochoroiditis

*Toxoplasma* retinochoroiditis may occur in patients with CD4 counts of <100 cells/ $\mu$ L and cause blurred vision, visual field defects, floaters, or flashing lights. In HIV-infected patients, ocular manifestations often appear after the infection of the central nervous system with *Toxoplasma* (see chapter *Toxoplasmosis*). Retinal examination may reveal yellow-white infiltrates without hemorrhage and active vitreous inflammation. Evaluation requires consultation with an HIV-experienced ophthalmologist. If toxoplasmosis is confirmed or strongly suspected, treatment should be initiated as quickly as possible.

### Neuro-Ophthalmologic Manifestations

Symptoms or signs of papilledema, optic neuritis, cranial nerve palsies, and visual field defects may indicate encephalopathy, increased intracranial pressure, neurosyphilis, toxoplasmosis, progressive multifocal leukoencephalopathy, meningitis, or central nervous system lymphomas. A thorough neurologic examination is required to determine whether additional diagnostic testing, such as imaging studies or cerebrospinal fluid testing, is needed in addition to ophthalmologic evaluation.

### Retinal Detachment

The patient may complain of flashes of light, sudden loss of vision, or both. This condition requires immediate referral to an emergency department.

## Patient Education

- Patients should report any changes in vision to their health care provider as soon as possible.
- Patients with CD4 counts of <50 cells/μL should be examined by an ophthalmologist at baseline and every 6 months thereafter.

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# Fatigue

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## Background

Fatigue is one of the most common and debilitating complaints of HIV-infected people, with an estimated prevalence of 33-88%. Fatigue is defined by the NIH Patient Reported Outcomes Measurement Information System (PROMIS) initiative as “mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that is likely to decrease one’s ability to carry out daily activities, including the ability to work effectively and to function at one’s usual level in family or social roles. Fatigue is divided conceptually into the experience of fatigue (such as its frequency, duration, and intensity), and the impact of fatigue upon physical, mental and social activities.” The consequences of severe fatigue may include curtailment of work and other activities, need for frequent breaks, limitations in involvement with family and friends, and difficulty completing even the simplest household chores.

In HIV-infected individuals, fatigue may be caused by comorbid conditions or by HIV itself. HIV-related fatigue is a broad term referring to fatigue that begins or significantly worsens after the patient is infected with HIV and that has no other identifiable causes. HIV-infected people with fatigue should be evaluated carefully for reversible causes, such as depression, anemia, hypothyroidism, hypogonadism, poor sleep quality, and medication adverse effects; if these are found, they should be treated aggressively. In some patients, fatigue may be related to advanced immunosuppression (e.g., low CD4 cell counts) or to high levels of circulating HIV virus. Unfortunately, for many patients, a specific cause of fatigue is not identified, and fatigue in many HIV-infected individuals may result from a complex interplay between physiologic and psychosocial variables. Recent research has examined genes that are predictive of low vs. high fatigue; abnormal neuronal circuitry involving striatal-cortical pathways that may play a role in HIV-related fatigue; prior use of didanosine or stavudine; and the presence of clinical lipodystrophy syndrome. From a psychosocial standpoint, stress, with its attendant anxiety and depression, seems to be the most consistent predictor of HIV-related fatigue.

## S: Subjective

The patient complains of tiredness, easy fatigability, a lack of energy, a need for frequent rest or naps, or waking in the morning feeling unrefreshed. The patient may report difficulty working, difficulty concentrating, inability to exercise without experiencing profound fatigue, or impairment in social relations because of fatigue.

Consider the following during the history:

- No objective clinical indicators exist for fatigue; thus, making a diagnosis of fatigue rests on subjective data.
- Fatigue assessment tools may help in diagnosing fatigue and estimating its severity. One such tool, the HIV-Related Fatigue Scale, was developed specifically for use with HIV-infected individuals; this assesses the intensity of fatigue (on the day of the assessment and during the previous week), the circumstances surrounding fatigue (including patterns), and the consequences of fatigue.
- Take a thorough history of the fatigue symptoms, including onset, duration, exacerbating and alleviating factors, and associated symptoms. Evaluate



for symptoms of other conditions that cause fatigue (e.g., hypothyroidism, hypogonadism, anemia, heart failure, poor nutrition).

- Depression can cause significant fatigue and is common among HIV-infected patients with fatigue. Screen the patient for depression. A single question – “Are you depressed?” – has been shown to be as valid and reliable as most depression instruments. See chapter *Major Depression and Other Depressive Disorders* for further information.
- Inquire about social history, specifically any life stressors including those related to housing status, work stress, and personal relationships.
- Evaluate the patient’s sleep patterns. HIV infection can interfere with sleep architecture early in the illness.
- Inquire about substance use or abuse.
- Obtain a list of all current medications, including herbal and over-the-counter preparations.
- Conduct a nutritional assessment.

## O: Objective

Check vital signs, including orthostatic blood pressure and heart rate measurements, if indicated. Perform a physical examination including evaluation of nutritional status, affect, conjunctivae and skin (for pallor), thyroid, lungs and heart, and deep tendon reflexes.

## A: Assessment

The differential diagnosis includes the following:

- Anemia
- Depression
- Hypogonadism
- Hypothyroidism
- Insomnia or poor-quality sleep
- Malnutrition
- Medication adverse effects (e.g., zidovudine, interferon)
- Opportunistic infections, malignancy, chronic hepatitis B or C, mononucleosis, other illnesses
- Pregnancy
- Substance use or abuse

## P: Plan

### Diagnostic Evaluation

To rule out reversible causes of fatigue, perform laboratory tests, including:

- Hemoglobin and hematocrit
- Thyroid function tests
- Testosterone (in both men and women)
- Pregnancy test, if applicable
- CD4 and HIV viral load (if not done recently), electrolytes, creatinine, and liver function tests

Fatigue assessment tools, as mentioned above, may be used to assess the intensity of fatigue, the circumstances surrounding fatigue, and the consequences of fatigue.

## Treatment

If testing reveals a specific cause of fatigue, treat appropriately. For example:

- Treat anemia, hypothyroidism, or hypogonadism, as indicated.
- Treat depression with antidepressant

medication, psychotherapy, or both; see chapter *Major Depression and Other Depressive Disorders*.

- Treat insomnia and review good sleep-hygiene practices with the patient; see chapter *Insomnia*.
- Refer for treatment of substance use or abuse, if possible.
- Provide counseling regarding any current life stressors that may be contributing to fatigue. Involve social work and case management services regarding housing issues or other social needs that may be contributing to fatigue.
- Treat malnutrition, ideally in conjunction with a nutritionist.
- Treat opportunistic infections and other illnesses. (See section *Comorbidities, Coinfections, and Complications*.)
- Control other symptoms that could be causing fatigue (e.g., diarrhea).
- If fatigue seems to be related to antiretroviral medication(s), weigh the benefits of the medication(s) against the possible adverse effects, and discuss these with the patient.

After appropriate evaluation, if the fatigue is thought to be related to HIV infection or if no specific cause is identified, consider the following:

- If HIV infection is inadequately controlled, particularly if the CD4 count is low or the HIV viral load is high, initiate or optimize antiretroviral therapy (ART), if otherwise appropriate.
- Patients taking effective ART may still experience HIV-related fatigue. Prepare patients for the possibility that fatigue may persist despite ART initiation.
- Encourage patients to track their patterns of fatigue with a fatigue diary. Once patients recognize their individual patterns, they can better cope with fatigue by planning their daily activities accordingly (e.g., performing the most strenuous tasks during times of

peak energy or staggering activities to avoid excessive fatigue).

- Ask patients what seems to aggravate their fatigue. This information, too, will help patients determine their patterns of fatigue and identify self-care actions they might take to avoid triggers that will worsen the fatigue.
- Recommend moderate exercise and frequent rest.
- Refer the patient to community-based agencies for assistance with housekeeping.
- Evaluate the need for occupational therapy (e.g., energy conservation techniques) or physical therapy (e.g., reconditioning and strengthening exercises).
- Medications such as stimulants (e.g., modafinil) may be helpful for some patients with severe or debilitating fatigue.

## Patient Education

- Fatigue is often unrelated to the CD4 cell count or HIV viral load. Teach patients not to dismiss feelings of fatigue if they have higher CD4 counts and lower viral loads. Encourage them to discuss their symptoms with a health care provider.
- For patients with depression, advise them that appropriate treatment may reduce fatigue.
- Help patients identify how current life circumstances and stressors may contribute to fatigue and encourage them to seek the appropriate social services to help manage appropriately.
- Talk to patients about their sleep habits and recommend changes, as appropriate, to improve their sleep hygiene.
- Prepare patients to accept the fact that their fatigue (in some cases) may be a chronic condition, in which case it can be best managed by maintaining open communication with their providers and remaining engaged in care.



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# Fever

## Background

Although fever may accompany HIV infection at various stages of disease, fever in a patient with a low CD4 count (<200 cells/ $\mu$ L) should prompt the clinician to rule out opportunistic infections.

### S: Subjective

The patient complains of persistent fever, or new-onset fever of  $>101^{\circ}\text{F}$  ( $38.3^{\circ}\text{C}$ ).

Assess the following during the history:

- Duration of fever
- Associated symptoms, including chills, sweats, weight loss
- Visual disturbances (see chapter *Eye Problems*)
- Nasal or sinus symptoms
- Asymmetric, tender, or new lymphadenopathy
- Cough or shortness of breath (see chapter *Pulmonary Symptoms*)
- Diarrhea, tenesmus (see chapter *Diarrhea*)
- Rash, lesions, soft-tissue inflammation
- Pain (for headache, see chapter *Headache*)
- Neurologic symptoms (see chapter *Neurologic Symptoms*)
- Vaginal or urethral discharge
- Other localizing symptoms
- Unprotected sexual contacts
- Recent injection drug use
- Intravenous line or venous access device
- Travel within the past 6-12 months
- Medications (as a cause of fever)
- Use of antipyretic agents including aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and acetaminophen; when was most recent dose taken?

### O: Objective

Document fever. Check other vital signs, including orthostatic measurements. Check weight and compare with previous values.

Search for evidence of an infectious focus. Perform a complete physical examination, including evaluation of the eyes (including fundus), sinuses, oropharynx, ears, lymph nodes, lungs and heart, abdomen, joints, genitals, uterus, rectum, skin, and neurologic system.

Review recent CD4 measurements, if available, to determine the patient's risk of opportunistic illnesses as a cause of fever.

### A: Assessment

The differential diagnosis varies depending on the CD4 count. Possibilities include the following:

#### Conditions More Likely with Low CD4 Count

- Aspergillosis
- Cryptococcosis
- Cytomegalovirus (CMV) infection
- Disseminated *Mycobacterium avium* complex (MAC)
- Disseminated histoplasmosis
- HIV infection itself
- Lymphoma, other neoplasms
- *Pneumocystis jiroveci* pneumonia (PCP)
- Toxoplasmosis
- Tuberculosis (atypical or extrapulmonary)

### Conditions That May Occur with Any CD4 Count

- Abscess, cellulitis
- Acute hepatitis
- Autoimmune process
- Bacteremia or sepsis
- Bacterial pneumonia or bronchitis
- Disseminated herpes simplex virus; chickenpox
- Drug-induced fever (common culprits include abacavir, nevirapine, sulfonamides, dapsone, penicillin, clindamycin, carbamazepine, phenytoin, barbiturates, and bleomycin)
- Endocarditis
- Immune reconstitution syndromes, related to opportunistic infections, are often associated with fever (see chapter *Immune Reconstitution Inflammatory Syndrome*)
- Influenza
- Otitis
- Malaria
- Pelvic inflammatory disease (PID)
- Sexually transmitted diseases
- Sinusitis
- Tuberculosis (pulmonary)
- Urinary tract infection (UTI)

### P: Plan

#### Diagnostic Evaluation

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. These may include the following:

- CD4 count (if not done recently) to help with risk stratification for opportunistic illnesses
- Complete blood count (CBC) with differential
- Blood cultures (bacterial, mycobacterial, fungal)
- Urinalysis, urine culture if UTI symptoms are present
- Liver transaminases, renal panel
- Chest X-ray
- Sinus films if indicated by symptoms and physical examination findings
- If respiratory symptoms and signs are present: sputum evaluation (Gram stain and acid-fast bacilli smear, evaluation for PCP), with culture of sputum for bacterial pathogens, acid-fast bacilli, viruses, and fungi as indicated; consider sputum induction or bronchoscopy if indicated
- Serum cryptococcal antigen, particularly if CD4 count is  $<100$  cells/ $\mu$ L and symptoms are consistent with cryptococcosis
- If neurological symptoms and signs are present: computed tomography (CT) or magnetic resonance imaging (MRI) of head, lumbar puncture
- For new lymphadenopathy: aspirate with culture (including acid-fast bacilli and fungal) and cytology
- For cytopenias: bone marrow aspirate and biopsy may be needed; see applicable treatment guidelines

- For fever of unknown origin (FUO), defined as persistent fever  $>101^{\circ}\text{F}$  for  $>3$  weeks without findings on initial workup, more intensive workup may be needed, such as lumbar puncture, other scans or biopsies; consult with a specialist in infectious diseases or an HIV expert to determine whether hospitalization or other laboratory tests are needed
- For patients who recently started abacavir or nevirapine, or other medications, rule out hypersensitivity reactions (see chapter *Adverse Reactions to HIV Medications*)

## Treatment

Once a diagnosis is made, appropriate treatment should be initiated. In seriously ill patients, presumptive treatment may be started while diagnostic tests are pending. In some cases, the source of fever cannot be identified. Consult with an HIV expert.

Symptomatic treatment may include NSAIDs (e.g., ibuprofen, naproxen), acetaminophen, and analgesics. Monitor for adverse gastrointestinal effects with NSAIDs. Cold compresses also can be used to relieve fever symptoms. Refer to a dietitian to avoid weight loss during the hypermetabolic state. See section *Comorbidities, Coinfections, and Complications* in this manual if an HIV-related cause is identified.

## Patient Education

- Patients should report any new fever to their health care provider. They should measure their temperature using a thermometer at home in order to report actual temperatures.
- Patients should know that fever usually is a sign that their bodies are battling an infection. Their health care providers may need to do special tests to find out what could be causing the fever.
- Many over-the-counter remedies are available to treat fevers. Patients should check with their care provider before taking these. Acetaminophen-containing products (e.g., Tylenol) generally are well tolerated. Persons with liver disease should use acetaminophen only as prescribed. NSAIDs (e.g., ibuprofen, naproxen) may be used, but they can cause adverse gastrointestinal effects, especially if taken without food. Patients should let their care provider know if they need to take these medicines for more than 2 or 3 days.

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# Headache

## Background

Headache in HIV-infected persons may result from many causes, particularly if the CD4 cell count is low. Possible causes include infections (opportunistic and other) and central nervous system malignancies, HIV-related systemic illnesses, and medication toxicity. In addition, headache may be caused by any of the processes that cause headache in HIV-uninfected individuals. New or severe headache should be evaluated carefully.

### S: Subjective

The patient complains of a new type of headache.

Determine the following during the history:

- History of headaches or migraines
- Characteristics of the headache (e.g., location, quality of pain, timing, duration)
- Recent head trauma
- Fever
- History of sinusitis
- Allergies
- Visual changes
- Dizziness, vertigo, nausea
- Mental status changes
- Seizures
- Focal or other neurologic symptoms (see chapter *Neurologic Symptoms*)
- New rashes or ulcerations
- Other symptoms
- Caffeine intake; recent changes in intake
- New medications (e.g., zidovudine, dolutegravir)
- Relief of headache by any medication
- Unprotected sex, new sex partner

### O: Objective

Perform a physical examination as follows:

- Check vital signs. Look for fever, orthostasis, and hypertension.
- Examine the head and neck for trauma, sinus tenderness, scalp or temple tenderness, and neck mobility; check lymph nodes.
- Check the eyes, including funduscopic examination, for lesions or papilledema.
- Look for oral lesions, dental abscess, thrush, and pharyngeal drainage.
- Examine the lungs for abnormal sounds.
- Check the skin, including palms and soles, for rashes or lesions.
- Perform a complete neurologic examination, including mental status examination.
- Review recent CD4 measurements, if available, to determine the patient's risk of opportunistic illnesses as a cause of headache.

**A: Assessment**

A partial differential diagnosis includes the following:

- Anemia
- Caffeine withdrawal
- Central nervous system lymphoma
- Cryptococcal meningitis
- Cytomegalovirus (CMV) meningoencephalitis or retinitis
- Dehydration
- Depression, anxiety disorder
- Fever
- Hypertension
- Medication adverse effect
- Migraine or cluster headache
- Neurosyphilis
- Other encephalitis
- Progressive multifocal leukoencephalopathy (PML)
- Sinusitis
- Stress or tension headache
- Systemic infection
- Temporal arteritis
- Toxoplasmic encephalitis
- Tuberculous meningitis; other meningitis

Other causes of headache unrelated to HIV should be considered.

**P: Plan****Diagnostic Evaluation**

Evaluation should include the following:

- CD4 cell count (if not done recently), to help with risk stratification for opportunistic illnesses
- Complete blood count with differential (if fever or suspected anemia); see chapter *Fever*
- Blood chemistries, including liver function tests, electrolytes, creatinine, glucose
- Serum cryptococcal antigen (if fever is present and CD4 count is <100 cells/μL); see chapter *Cryptococcal Disease*
- *Toxoplasma* immunoglobulin G (consider if previously negative and CD4 count is <100 cells/μL; may indicate risk of toxoplasmosis); see chapter *Toxoplasmosis*
- Syphilis testing: rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test; see chapter *Syphilis*

When indicated, also consider:

- Computed tomography (CT) scan with contrast or magnetic resonance imaging of the head; see chapter *Neurologic Symptoms*
- Lumbar puncture with cerebrospinal fluid (CSF) studies to include opening pressure, cell count, chemistries, bacterial cultures; fungal and acid-fast bacilli evaluations and cultures; India ink stain; cryptococcal antigen, VDRL, as indicated
- Sinus imaging
- Erythrocyte sedimentation rate, if temporal arteritis is suspected

## Treatment

- Once a diagnosis is made, appropriate treatment should be initiated. In seriously ill patients, presumptive treatment may be initiated while diagnostic test results are pending. In some cases, the source of headache cannot be identified. Consult with an HIV expert or a neurologist.
- Refer to disease-specific treatment guidelines or primary care management guidelines as appropriate.
- Treat symptomatically with nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, or narcotics, if indicated, to control pain.

## Patient Education

- Headache can be a sign of an opportunistic infection, especially in patients with low CD4 cell counts. Patients should notify their health care provider if they develop a new headache.
- Providers should inform patients that they may have to do additional tests to determine the cause of the headache.
- Many over-the-counter remedies are available for headache. Patients should check with their health care provider before taking these. Acetaminophen-containing products (e.g., Tylenol) generally are well tolerated. Persons with liver disease should use acetaminophen only as prescribed. NSAIDs (e.g., ibuprofen, naproxen) may be used, but these agents can cause adverse gastrointestinal effects, especially if taken without food. Patients should inform their care provider if they need to take these medicines for more than 2 or 3 days.

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# Lymphadenopathy

## Background

Lymphadenopathy is very common among HIV-infected individuals and may occur at any stage of HIV infection. It may be the first indication of a serious local or systemic condition, and it should be evaluated carefully. Rapid enlargement of a previously stable lymph node or a group of nodes requires evaluation to identify the cause and to determine whether treatment is needed. Similarly, nodes that are abnormal in consistency, tender to palpation, fluctuant, asymmetrical, adherent to surrounding tissues, or accompanied by other symptoms should be evaluated promptly.

Lymphadenopathy may be generalized or localized and usually is characterized by lymph nodes that are >1 cm in diameter. A multitude of conditions can cause lymphadenopathy, including HIV itself, opportunistic or other infections, and malignancies. The likely causes of lymphadenopathy, and thus the diagnostic workup, will depend in part on the patient's degree of immunosuppression. The risk of opportunistic and certain malignant conditions increases at lower CD4 cell counts (see chapter *Risk of HIV Progression/Indications for ART*).

Many individuals with primary HIV infection (see chapter *Early HIV Infection*) have generalized lymphadenopathy that may resolve or may persist for months to years. If lymphadenopathy of >2 cm in size occurs in two or more noncontiguous sites and persists for more than 3 months, and if appropriate evaluation reveals no other cause, the patient is diagnosed with persistent generalized lymphadenopathy (PGL). PGL usually is caused by follicular hyperplasia from chronic HIV infection. Antiretroviral therapy (ART) should be initiated or optimized, but as long as enlarged nodes are stable in number, location, and size, persons with PGL require no specific management other than monitoring of nodes at each physical examination. Changes in the character of the lymph nodes should prompt further evaluation. Rapid involution of PGL may occur with advanced HIV disease and is a poor prognostic sign.

## S: Subjective

The patient complains of new, worsening, or persistent glandular swellings in the neck, axilla, groin, or elsewhere.

Ascertain the following during the history:

- Symptoms that accompany the lymphadenopathy, particularly constitutional symptoms such as fever, sweats, fatigue, and unintentional weight loss
- Localized symptoms or conditions that involve areas of the body with lymphatic drainage into the area of abnormal lymph nodes (e.g., in the case of axillary lymphadenopathy, ask about breast masses and skin conditions or trauma involving the arm)
- A full review of systems
- HIV-related or other malignancies, opportunistic illnesses
- Recent travel, country or region of origin, disease exposures (e.g., tuberculosis [TB], sexually transmitted diseases [STDs]), and risk behaviors (e.g., injection drug use)
- Recent initiation of ART (may indicate immune reconstitution inflammatory syndrome [IRIS])
- Trauma or injury (including cat scratches)
- Exposure to household pets
- Current medications



**O: Objective**

- Review recent CD4 cell counts and HIV viral load measurements.
- Check vital signs.
- Perform a complete examination of lymph nodes, including the cervical, submandibular, supraclavicular, axillary, epitrochlear, and inguinal sites. Document the location, size, consistency, mobility, and presence or absence of tenderness of all abnormal nodes. In cases of localized lymphadenopathy, examine the area drained by the node.
- Check for hepatosplenomegaly.
- Perform a focused examination (e.g., lung, breast, skin, genitals) to identify signs of local or systemic illness.

**A: Assessment**

The differential diagnosis of lymphadenopathy in HIV-infected patients depends in part on the degree of immunosuppression. For further information, see chapter *Risk of HIV Progression/Indications for ART*.

**Infectious Causes****Generalized lymphadenopathy**

- HIV infection, including PGL
- Mononucleosis; Epstein-Barr virus
- *Mycobacterium avium* complex
- TB
- Cytomegalovirus
- Secondary syphilis
- Toxoplasmosis

- Histoplasmosis, other fungal diseases
- *Bartonella* infection
- Hepatitis B
- Lyme disease
- Widespread skin infections
- IRIS involving various infections
- Follicular hyperplasia
- Castleman disease

**Localized lymphadenopathy**

- Any of the above
- Oropharyngeal and dental infections
- Cellulitis or abscesses
- TB (scrofula)
- Chancroid
- Chlamydia (lymphogranuloma venereum [LGV])
- Other STDs

**Neoplastic Causes**

- Lymphoma
- Acute and chronic lymphocytic leukemias
- Other malignancy; metastatic cancer
- Kaposi sarcoma

**Other Causes**

- Reactive process (benign)
- Sarcoidosis
- Hypersensitivity reaction to medications
- Serum sickness
- Rheumatoid arthritis

## P: Plan

### Diagnostic Evaluation

After the history and physical examination, the cause of lymphadenopathy may be clear and further diagnostic testing may not be necessary. If the cause of the lymphadenopathy is still uncertain, perform diagnostic testing as indicated by the patient's presentation. This may include the following tests:

- CD4 count (with or without HIV viral load), to determine the risk of opportunistic illnesses
- Complete blood count with differential; liver function tests; urinalysis
- Chest X-ray
- TB screening (tuberculin skin test [TST] or interferon-gamma release assay [IGRA])
- Syphilis screening (rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL] test)
- Blood cultures, if patient is febrile (bacterial, mycobacterial, and fungal, as indicated)
- Testing for specific infections if suspected (e.g., *Bartonella*, LGV)

If a node is large, fixed, nontender, or otherwise worrisome, or if the diagnosis is unclear after initial evaluation, fine-needle aspiration (FNA) biopsy may provide a diagnosis. If FNA is nondiagnostic (false-negative results are relatively common), obtain an excisional biopsy for definitive evaluation. Biopsy specimens should be sent for bacterial, mycobacterial, and fungal cultures; acid-fast staining for mycobacteria; and cytologic examination.

If a node is large, inflamed, tender, or fluctuant, and a bacterial infection is suspected, consider initiating empiric

antibiotic treatment and monitoring the patient over the course of 1-2 weeks. If the node does not respond to antibiotic treatment or the patient becomes more symptomatic, arrange for FNA or open biopsy to establish the diagnosis.

### Treatment

Treatment will depend on the cause of lymphadenopathy. Refer to section *Comorbidities, Coinfections, and Complications* or to OI management guidelines as appropriate. In the case of HIV-related lymphadenopathy, ART may be effective.

### Patient Education

- Lymphadenopathy may come and go throughout the course of HIV infection, but it may be a sign of a serious condition.
- Advise patients to notify their care provider if lymph nodes increase in size or change in character.

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# Nausea and Vomiting

## Background

Nausea with or without vomiting, and occasionally vomiting without nausea, can occur at any stage of HIV infection. Nausea is a common adverse effect of many antiretroviral (ARV) and other medications, and it often occurs within weeks of starting new medications. In some cases, nausea causes significant discomfort and may interfere with medication adherence. Nausea and vomiting also may be symptoms of a serious complication of ARV therapy, or signs of an opportunistic infection or neoplasm in patients with late-stage AIDS. Clinicians must identify the cause of nausea and vomiting and initiate appropriate treatment.

## S: Subjective

The patient experiences nausea with or without vomiting, or vomiting without nausea.

Ascertain the following during the history:

- Duration of symptoms
- Characteristics, timing, and precipitating factors
- Vomiting, including hematemesis
- Diarrhea
- Abdominal pain
- Fever
- Jaundice
- Lightheadedness, dizziness, vertigo, or orthostatic symptoms
- Polyuria
- Polydipsia
- Headache
- Changes in vision
- Neck stiffness
- Pruritus
- Medications, new and ongoing
- Nutritional supplements and non-prescription medications
- Possibility of pregnancy (for women) (e.g., missed menses)
- Alcohol intake, substance use or abuse
- History of:
  - Hepatitis
  - Kidney disease
  - Pancreatitis
  - Cytomegalovirus
  - Central nervous system (CNS) infections, including toxoplasmosis, cryptococcosis, chronic meningitis
  - CNS lymphoma

## O: Objective

Check vital signs, including orthostatic blood pressure and heart rate measurements.

Conduct a thorough physical examination, including evaluation of the following:

- Skin turgor
- Eyes and fundi (retinal abnormalities such as papilledema)
- Oropharynx (dryness of oral mucosa, thrush, ulcerations)
- Neck (stiffness or other signs of meningeal irritation)
- Abdomen (tenderness, distention, masses, organomegaly)
- Pelvis (tenderness, masses)

- Neurologic system (mental status, focal neurologic abnormalities)

Review recent CD4 measurements, if available, to determine the patient's risk of opportunistic illnesses.

## A: Assessment

A partial differential diagnosis includes the following conditions:

- Medication effect or reaction
- Foodborne illness
- Viral or other infectious gastroenteritis
- Pancreatitis
- Hepatitis, infectious or drug related (see chapters *Hepatitis B Infection* and *Hepatitis C Infection*)
- Appendicitis
- Esophagitis (see chapter *Esophageal Problems*)
- Lactic acidosis attributable to nucleoside analogues
- Pregnancy
- Adrenal insufficiency
- CNS lymphoma
- Meningitis
- Uremia
- Diabetic ketoacidosis
- Influenza
- Pelvic inflammatory disease (see chapter *Pelvic Inflammatory Disease*)
- Myocardial infarction

## P: Plan

### Diagnostic Evaluation

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. Tests may include the following:

- Complete blood count with differential
- Electrolytes, creatinine, blood urea nitrogen
- Glucose
- Amylase and lipase if symptoms of pancreatitis are present
- Liver function tests and hepatitis serologies for possible acute or chronic hepatitis
- Blood cultures and other fever workup as needed (see chapter *Fever*)
- Computed tomography scan of the brain if neurologic symptoms are present (see chapter *Neurologic Symptoms*)
- Cortisol and cosyntropin stimulation test if indicated (e.g., fatigue, weakness, unexplained abdominal pain, weight loss, orthostasis; usually in late-stage AIDS)
- If odynophagia or dysphagia is present, see chapter *Esophageal Problems*
- Lactic acid levels if lactic acidosis is suspected
- Pregnancy test if indicated
- Electrocardiogram if patient has chest pain or suspicious symptoms

Consult with an HIV expert to determine whether hospitalization or other laboratory tests are needed.

## Treatment

Once the diagnosis is made, appropriate treatment should be initiated. In seriously ill patients, presumptive treatment may be started while diagnostic test results are pending. See appropriate chapters in section *Comorbidities, Coinfections, and Complications* and relevant guidelines.

In the case of significant adverse effects from ARVs or other medications, substitute a less-emetogenic ARV for the problematic medication, if possible (without compromising the efficacy of the treatment regimen). In the case of serious or life-threatening medication toxicities (e.g., lactic acidosis or abacavir hypersensitivity reaction), discontinue the problematic medication (see chapter *Adverse Reactions to HIV Medications*).

After the workup and exclusion of life-threatening illness, symptomatic treatment can be considered. If nausea and vomiting are attributable to medications that are vital to the patient, and these complications are not life-threatening, antiemetic therapy may be the best treatment. Chronic therapy is not always necessary. Some patients obtain adequate relief by breaking the “nausea cycle” with effective antiemetics for 1-2 days and then establishing meals or snacks with medications. Patients with dehydration may require administration of fluids (PO or IV) to relieve nausea. For patients with chronic nausea resulting in weight loss, refer to a nutritionist for assessment and nutritional support.

## Symptomatic treatment

Consider the following strategies for symptomatic treatment:

- For nausea that occurs in relation to an event or action (e.g., after taking ARVs) antiemetics may be given preemptively (e.g., 30 minutes beforehand).
- Ginger capsules have proven effective in clinical trials for the management of pregnancy-related and chemotherapy-related

nausea. Foods and beverages containing ginger (e.g., tea, cookies, ginger ale, candies) may help provide relief.

- Promethazine (Phenergan) may be given as a 12.5-25 mg PO tablet Q4-6H as needed. For patients unable to tolerate the PO formulation, promethazine suppositories (12.5 or 25 mg) may be used.
- Prochlorperazine (Compazine) may be given as a 5 mg or 10 mg PO tablet, or a 25 mg rectal suppository, Q6-8H as needed. Extended-release spansule, 10 mg Q12H or 15 mg QAM, also can be considered.
- Lorazepam (Ativan) may be given as a 0.5 mg PO tablet 30 minutes before taking medications for symptoms of anticipatory nausea. Patients with anticipatory nausea develop significant nausea or vomiting when even thinking about medications or reaching for the medications.
- Dronabinol (Marinol) may relieve nausea, especially when nausea is accompanied by a loss of appetite. This remedy is best tolerated by patients who have tolerated inhaled marijuana. The starting dosage is 2.5 to 5 mg BID or TID.
- 5-Hydroxytryptamine (5-HT<sub>3</sub>) receptor antagonists such as dolasetron 50 mg and 100 mg, granisetron 1 mg, and ondansetron 4 mg and 8 mg are highly effective in relieving severe nausea and vomiting resulting from chemotherapy and other causes. However, access to these medications is limited by their cost. Their use should be considered a short-term strategy or reserved for cases of nausea/vomiting refractory to other antiemetics.
- Metoclopramide (Reglan) may be used to enhance gastrointestinal motility in patients who experience nausea and vomiting caused by gastroparesis. The typical PO dose is 5-10 mg Q4-6H, or it can be taken TID with meals if the nausea or vomiting is associated with eating.

- H2 antagonists or proton pump inhibitors may be helpful in treating nausea/vomiting related to gastritis or acid reflux (caution: these agents interfere with absorption of atazanavir and rilpivirine; consult dosing recommendations); see chapter *Esophageal Problems* and 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* (see Appendix).
- Many patients wonder whether they should take their medicines again if they vomit after taking a dose. Generally, the medicines are still in the body unless the pills actually come back up. Patients should call their health care provider if they have any questions.
- Ginger may help to relieve nausea. Ginger can be taken in a variety of ways, including ginger ale, tea, cookies, candies, and ginger capsules. Patients can choose the form of ginger that works best for them.

## Patient Education

- Nausea and vomiting can have many different causes. Patients should let their health care provider know if they are having these symptoms so that the most likely cause can be determined.
- Patients should stay nourished and well hydrated even if they are experiencing nausea and vomiting. Eating small, frequent meals may be best tolerated, while avoiding dairy products, spicy or greasy foods, and high-fat meals. Taking medications with food may reduce symptoms of nausea (note that some medications must be taken on an empty stomach).
- Patients should not stop taking any of their medications without first discussing it with their health care provider. Many medications must be continued despite nausea. Nausea and vomiting owing to ARVs may resolve or become tolerable over time.

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# Neurologic Symptoms

## Background

The nervous system may be a site of complications throughout the course of HIV infection, and neurologic complaints are common among HIV-infected individuals. Neurologic symptoms may be caused by many factors, including infections (opportunistic and other), central nervous system (CNS) malignancies, medication toxicities, comorbid conditions (e.g., diabetes, cerebrovascular disease, chronic hepatitis, mental illness), and nervous system injuries related to HIV itself.

The risk of some conditions, such as CNS infection, malignancy, and dementia, increases with advancing immunosuppression, and the CD4 cell count will help to stratify the patient's risk of opportunistic illnesses (see Table 1 in chapter *Risk of HIV Progression/Indications for ART*). This chapter presents a general approach to neurologic symptoms in HIV-infected patients, with reference to other chapters in this manual for more detailed reading. For information on peripheral neuropathy, see chapter *Pain Syndrome and Peripheral Neuropathy*; for information on neurocognitive disease, see *HIV-Associated Neurocognitive Disorders*.

## S: Subjective

The patient, or a friend or family member on his or her behalf, reports new neurologic symptoms such as pain, headache, seizures, altered mental status, or weakness.

Ascertain the following during the history:

- Onset and duration: rapid (hours to days), subacute, chronic
- Characteristics of the symptoms (e.g., location, quality, timing)
- Progression or stability of symptoms
- Constitutional symptoms: fever, night sweats, unintentional weight loss
- Associated symptoms, including other neurologic, muscular, psychiatric, or behavioral symptoms
- Recent trauma to the head or other area
- Visual changes, photophobia
- Dizziness, vertigo
- Mental status changes (including changes in behavior, personality, or cognition; short-term memory loss; mental slowing; reading comprehension difficulties; changes in personal appearance and grooming habits)
- Seizures (description, duration, number)
- Pain
- Sensory symptoms
- Weakness (distinguish weakness from fatigue or pain; determine whether bilateral or focal, proximal or distal)
- Bowel or bladder changes
- Rash or ulcerations
- Medications: current, past, and recently initiated medications, including antiretroviral (ARV) medications
- Alcohol or drug use; date of last use
- Exposures (sexual, environmental), travel history
- Psychiatric history and past psychiatric care
- Most recent CD4 cell count and HIV viral load, previous AIDS-defining illnesses
- Functional impact of the symptoms: social functioning, ability to work and perform activities of daily living

Differentiate delirium and dementia. Delirium presents as acute onset of clouded sensorium, disturbed and fluctuating



level of consciousness, disorientation, cognitive deficits, and reduced attention, sometimes with hallucinations. Delirium often is caused by medication toxicities, infections, hypoxia, hypoglycemia, electrolyte imbalances, or mass lesions, and it frequently is correctable. Dementia emerges more gradually and is characterized by cognitive impairment and behavioral, motor, and affective changes. See chapter *HIV-Associated Neurocognitive Disorders*.

## O: Objective

- Check vital signs (temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) and orthostatic measurements.
- Perform a careful physical examination as guided by the history, with special attention to the following:
  - General appearance: mood, affect, mannerisms
  - Head and neck: signs of trauma, sinus tenderness, lymph node status, neck mobility
  - Eyes, including fundi: lesions, papilledema
  - Lungs, heart: abnormal sounds
  - Extremities: muscle tone and bulk
  - Skin, mucous membranes: rash, lesions
- Conduct a thorough neurologic examination, including cranial nerves, motor function, sensory function, coordination, gait, and deep tendon reflexes.
- Conduct a mental status examination.
- Review recent CD4 measurements, if available, to determine the patient's risk of opportunistic illnesses.

## A: Assessment

The differential diagnosis of neurologic abnormalities in patients with HIV infection may be broad, particularly if the CD4 count is low. Both HIV-related and HIV-unrelated causes should be considered; remember that more than one cause of symptoms may be present.

## Possible Causes of Neurologic Abnormalities

### Causes related to the cerebrum or cranial nerves

- Toxoplasmic encephalitis
- Primary CNS lymphoma
- Cryptococcal meningitis
- Cytomegalovirus (CMV) encephalitis
- Other meningitis (bacterial, tuberculous, fungal, viral)
- Progressive multifocal leukoencephalopathy (PML)
- Neurosyphilis
- CNS coccidioidomycosis, histoplasmosis
- HIV-related dementia
- Cerebrovascular accident; stroke
- Metabolic abnormalities, including hypo- or hyperglycemia, electrolyte abnormalities
- Alcohol or drug intoxication or withdrawal (medications or illicit drugs); chronic alcohol abuse
- Medication adverse effects (e.g., efavirenz, corticosteroids, anticholinergics, many others)
- Depression, mania, anxiety, psychosis



### Causes related to the spinal cord, nerve roots, peripheral nerves, and muscle

- Inflammatory demyelinating polyneuropathy (e.g., Guillain-Barré syndrome)
- Polyradiculitis (e.g., CMV, herpes simplex virus)
- Vitamin deficiency
- Myositis
- Myopathy (e.g., owing to zidovudine)
- Myelopathy (e.g., HIV vacuolar myelopathy)
- Epidural abscess or mass
- Mononeuritis multiplex
- Lactic acidosis
- Electrolyte abnormality (e.g., hypokalemia)
- Peripheral neuropathy
- Distal sensory polyneuropathy
- Antiretroviral toxic neuropathy (especially stavudine, didanosine)
- Other neuropathy (e.g., owing to diabetes, alcohol, medications [isoniazid, dapsone, many others])

Note that organic causes of neurologic symptoms must be ruled out before concluding that symptoms are psychiatric in nature.

### P: Plan

#### Diagnostic Evaluation

Unstable or seriously ill patients should be hospitalized for evaluation and treatment. Criteria for hospitalization include acutely altered mental status, fever with focal neurologic findings, and new or unstable seizures.

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. This may include the following:

- Establish the CD4 count (if not done recently) to help with risk stratification for opportunistic illnesses.
- Determine which laboratory tests are appropriate, depending on the patient's presentation. The initial evaluation often includes a complete blood count with differential and monitoring of electrolyte and glucose levels.
  - In patients with CNS symptoms or signs and low CD4 counts ( $<100$  cells/ $\mu$ L), check serum levels of *Toxoplasma* antibody (IgG) if not previously checked. Check serum cryptococcal antigen (CrAg) titer.
  - In patients with symptoms of neuropathy or dementia, check serum levels of vitamin B12 and thyroid-stimulating hormone (TSH).
  - In patients with cranial nerve abnormalities, meningoencephalitis, symptoms of dementia, or any symptoms of neurosyphilis, check syphilis serology by rapid plasma reagin (RPR), Venereal Disease Research Laboratory (VDRL) test, or treponemal enzyme immunoassay (see chapter *Syphilis*).
- When CNS symptoms or signs are present, brain imaging by computed tomography (CT) scan with contrast is usually adequate as the initial test. Magnetic resonance imaging (MRI) is the modality of choice if the neurologic examination is nonfocal or if physical examination suggests a lesion in the posterior fossa.
- For patients with fever and CNS findings, perform lumbar puncture (LP) with cerebrospinal fluid (CSF) sampling. CT or MRI should be performed before the LP, if possible, to rule out a mass lesion that could cause herniation.
- Record the opening pressure, and send CSF for cell count and differential with protein and glucose measurements. Depending on the clinical suspicion, the fluid also should be sent for bacterial culture, India ink stain for fungal organisms (75-85% sensitive), acid-fast bacilli smear and culture, VDRL test, and CrAg titer (95% sensitive).

- If CMV is suspected, perform polymerase chain reaction (PCR) for CMV DNA in the CSF.
- For suspected drug or alcohol use, perform urine or serum toxicology screen. (Note that alcohol usually has been metabolized by the time withdrawal symptoms set in, typically 7-48 hours after the last alcohol intake.)
- For new-onset seizures, perform an electroencephalogram (EEG).
- Consult with neurology specialists if the workup or the diagnosis is in question.
- Advise patients who have seizures that driving and other potentially dangerous activities will be prohibited until the condition is stable.
- Counsel patients to avoid substances that impair the nervous system, such as alcohol and recreational drugs.
- If a patient is forgetful, educate other members of the household about the medication regimen and help devise a plan for adherence to medications and appointments.

## Treatment

- Specific treatment will depend on the cause of neurologic symptoms. Consult relevant chapters in this manual. For complex cases, consult with an HIV-experienced neurologist.

## Patient Education

- Inform patients that keeping the CD4 count >200 cells/ $\mu$ L (and preferably higher) with ART is the best way to prevent most HIV-associated neurologic diseases.
- Advise patients to take prophylaxis, as appropriate, to prevent opportunistic infections.
- When an antibiotic treatment is prescribed, advise patients to complete the entire regimen to prevent relapse of symptoms. Long-term treatment (secondary prophylaxis) will be needed to prevent recurrence of certain infections.

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# Pulmonary Symptoms

## Background

Shortness of breath and cough are manifestations of common acute or chronic respiratory diseases, but also may be symptoms of HIV-related opportunistic infections. Further, these symptoms may indicate nonpulmonary conditions such as anemia, cardiovascular disease, and sinusitis, or adverse effects of medications such as angiotensin-converting enzyme inhibitors (ACEIs).

The onset and duration of symptoms, and the presence or absence of other factors such as sputum production, fever, and weight loss, will guide the evaluation. In addition, the patient's CD4 cell count will establish a context for the evaluation, because it will help to stratify the risk of opportunistic infections.

## S: Subjective

The patient complains of dyspnea or cough.

Determine the following factors relating to the patient's history:

### Recent History

- Onset and duration of symptoms: rapid (hours to days), subacute, chronic
- Progression or stability of symptoms
- Dyspnea at rest or with exertion
- Cough: productive (character of sputum), hemoptysis
- Associated symptoms (e.g., chest pain, pleuritic pain)
- Constitutional symptoms: fever, night sweats, unintentional weight loss
- Sinus congestion, facial tenderness, postnasal discharge, sore throat
- Orthopnea, paroxysmal nocturnal dyspnea (PND), peripheral edema
- Wheezing

## Past History

- CD4 nadir, current CD4 count
- If the CD4 count is  $<200$  cells/ $\mu$ L, ask whether the patient is taking *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis (primary or secondary); if taking PCP prophylaxis and adhering to the regimen, the diagnosis of PCP is less likely
- Tuberculosis (TB): date and result of tuberculin skin test (TST) or interferon-gamma release assay (IGRA), risk factors for *Mycobacterium tuberculosis* infection
- PCP, bacterial or other pneumonia, bronchitis
- Smoking (and secondhand smoke exposure), pack-years, related symptoms
- Cardiovascular diseases, including congestive heart failure, coronary heart disease, arrhythmia, pulmonary hypertension
- Asthma, emphysema
- Pollen, dander, or dust allergies
- Drug allergies, specifically to penicillins and sulfa drugs
- Medications (e.g., ACEIs)
- Travel history (exposure to regions endemic for particular infections, such as coccidioidomycosis or histoplasmosis)
- Use of inhaled stimulants, injection drugs

- Prolonged exposure (via inhalation) to chemicals or other harmful pulmonary irritants (e.g., asbestos)

## O: Objective

Check vital signs, oxygen saturation (resting and after exercise), and weight.

Conduct a thorough physical examination that includes evaluation of the following:

- Ears, nose, oropharynx
- Neck
- Lungs
- Heart
- Extremities

Note: If patients are coughing, strongly consider having them wear a surgical mask in the clinic or office until TB or other transmissible infection is ruled out. Covering both the nose and the mouth should prevent the discharge of infectious particles into the environment.

## A: Assessment

The differential diagnosis of pulmonary symptoms is broad (see Table 1). Both HIV-related and HIV-unrelated causes should be considered; the patient's risk of HIV-related causes is strongly influenced by the CD4 count. More than one cause of symptoms may be present.

**Table 1. Partial Differential Diagnosis of Pulmonary Symptoms**

CD4 Cell Count	Possible Cause
Any Count	<ul style="list-style-type: none"> <li>• Upper respiratory tract illness</li> <li>• Upper respiratory tract infection (URI)</li> <li>• Sinusitis</li> <li>• Pharyngitis</li> <li>• Acute or chronic bronchitis</li> <li>• Bacterial pneumonia</li> <li>• TB</li> <li>• Influenza</li> <li>• Chronic obstructive pulmonary disease</li> <li>• Reactive airway disease, asthma</li> <li>• Pulmonary embolus</li> <li>• Congestive heart failure</li> <li>• Pulmonary hypertension</li> <li>• Pneumothorax</li> <li>• Bronchogenic carcinoma</li> <li>• Non-Hodgkin lymphoma</li> <li>• Anemia</li> <li>• Gastroesophageal reflux (may cause cough)</li> <li>• Lactic acidosis</li> <li>• Medication adverse effect</li> </ul>
≤500 cells/μL	<ul style="list-style-type: none"> <li>• Bacterial pneumonia (recurrent)</li> <li>• Pulmonary <i>Mycobacterium pneumonia</i> (nontuberculous)</li> </ul>
≤200 cells/μL	<ul style="list-style-type: none"> <li>• PCP</li> <li>• <i>Cryptococcus neoformans</i> pneumonia or pneumonitis</li> <li>• Bacterial pneumonia (associated with bacteremia or sepsis)</li> <li>• Disseminated or extrapulmonary TB</li> </ul>
≤100 cells/μL	<ul style="list-style-type: none"> <li>• Pulmonary Kaposi sarcoma</li> <li>• Bacterial pneumonia (risk of gram-negative bacilli and <i>Staphylococcus aureus</i> is increased)</li> <li>• <i>Toxoplasma</i> pneumonitis</li> </ul>
≤50 cells/μL	<ul style="list-style-type: none"> <li>• Disseminated histoplasmosis</li> <li>• Disseminated coccidioidomycosis</li> <li>• Cytomegalovirus pneumonitis</li> <li>• Disseminated <i>Mycobacterium avium</i> complex</li> <li>• Disseminated <i>Mycobacterium</i> (nontuberculous)</li> <li>• <i>Aspergillus</i> pneumonia</li> <li>• <i>Candida</i> pneumonia</li> </ul>

Adapted from: Huang L. *Pulmonary Manifestations of HIV* (Table 4). In: Coffey S, Volberding PA, eds. *HIV InSite Knowledge Base* [textbook online]; San Francisco: UCSF Center for HIV Information; January 2009. Available at [hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-04-01-05](http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-04-01-05). Accessed December 1, 2013.

**P: Plan****Diagnostic Evaluation**

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. This may include the following:

- Chest X-ray, especially if the patient has abnormal findings on chest examination, fever, or weight loss, or if the CD4 count is  $<200$  cells/ $\mu$ L. Consider further imaging such as chest computed tomography (CT) scan or high-resolution chest CT (HRCT) if chest X-ray result is unremarkable in a setting of suspected PCP or persistent symptoms, or if there is question of pulmonary nodules or suspected empyema.
- Arterial blood gas (ABG) on room air, particularly if PCP is suspected, or if the oxygen saturation is low.
- Complete blood count and white blood cell (WBC) count with differential, metabolic panel, and lactate dehydrogenase (LDH).
- If fever is present (especially temperature  $>38.5^{\circ}\text{C}$ ), obtain routine blood cultures (two specimens) for bacteria. If the CD4 count is  $<50$  cells/ $\mu$ L, obtain blood culture for acid-fast bacilli (AFB); if  $<100$  cells/ $\mu$ L, check the serum level cryptococcal antigen (CrAg) and consider checking urine *Histoplasma* antigen.
- Induced sputum (outside, or in a negative-pressure room or area that is safely vented to the outside, to prevent TB aerosolization) for AFB smear and cultures (three specimens), Gram stain and bacterial cultures, PCP stains, fungal stains and cultures, and cytology, as indicated.
- CD4 count and HIV viral load, if recent values are not known.
- Bronchoscopy with bronchoalveolar lavage (BAL) or biopsy if sputum studies are negative, if the diagnosis is unclear after initial evaluation or if the patient is not responsive to empiric therapy.
- Pulmonary function tests if no infectious or HIV-related pulmonary diagnosis is suspected and symptoms persist.
- Lactate level if lactic acidosis is suspected (e.g., nausea, tachypnea, abdominal pain, fatigue, in the setting of long-term nucleoside analogue therapy).
- Toxicology screen if symptoms are suspected to be related to recent drug use (e.g., crack cocaine pneumonitis).

**Treatment**

Once the diagnosis is made, appropriate treatment should be initiated. In seriously ill patients, presumptive treatment may be started while diagnostic test results are pending. See the appropriate chapter in section *Comorbidities, Coinfections, and Complications* or relevant guidelines. In some cases, the source of dyspnea or cough cannot be identified. In these cases, consult with an HIV expert or a pulmonologist.

## Patient Education

- Shortness of breath and cough can be signs of an opportunistic illness, especially in patients with low CD4 counts. Patients should notify their health care provider if they develop new or worsening symptoms.
- Patients taking antibiotics should be instructed to take their medications exactly as directed and to call their health care provider if they experience worsening fevers, shortness of breath, inability to take the prescribed medications, or other problems.
- Counsel smokers about the importance of smoking cessation; refer to tobacco cessation programs and prescribe cessation supports, as indicated; see chapter *Smoking Cessation*.
- Counsel drug users (particularly those who smoke or inject drugs) regarding the impact of illicit drugs on their overall health and especially their lungs; refer to appropriate cessation programs or rehabilitation programs.

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# Vaginitis/Vaginosis

## Background

Vaginitis is defined as inflammation of the vagina, usually characterized by a vaginal discharge containing many white blood cells (WBCs); it may be accompanied by vulvar itching and irritation. Vaginosis presents with increased vaginal discharge without inflammation. Vaginitis usually is caused by an infection, but may be caused by other factors, such as chemicals or irritants. Vaginal infections are common among HIV-infected women. The presence of vaginal infections or inflammation, in the case of bacterial vaginosis in particular, may facilitate acquisition of HIV and other sexually transmitted diseases (STDs), and trichomoniasis may facilitate HIV transmission to HIV-uninfected partners. This chapter focuses on two of the most common types of vaginal infections: trichomoniasis and bacterial vaginosis (BV). For information on the topic of vulvovaginal candidiasis, see chapter *Candidiasis, Vulvovaginal*.

## S: Subjective

The patient complains of vaginal discharge with or without odor, itching, burning, pelvic pain, vulvar pain, or pain during intercourse.

Take a focused history, including the following:

- Duration of symptoms
- Sexual history, especially recent new partners, unprotected sex
- Relationship of symptoms to sexual contacts
- Contraceptive use, especially:
  - Vaginal contraceptive film
  - Other products containing nonoxynol-9 (N-9)
  - Condoms; type of condoms
- Use of feminine hygiene products (e.g., sprays, deodorants)
- Douching
- Use of perfumed toiletries (e.g., bath salts, scented toilet tissue, or sanitary napkins)
- Use of any vaginal creams
- Postcoital bleeding
- Vulvar pain
- Pain or burning during urination

- Pain with intercourse
- Recent antibiotic use
- History of STDs, pelvic inflammatory disease (PID)
- Medications, including supplements

## O: Objective

Perform a focused physical examination of the external genitalia, including perineum and anal area, for the following:

- Inflammation
- Edema
- Excoriation
- Lesions

Perform speculum examination for:

- Discharge (note color, quality; note that the character of the discharge is not diagnostic)
- Erythema, edema, erosions, lesions
- Cervical friability
- Foreign body

Perform a bimanual examination for masses or tenderness, if indicated.



## A: Assessment

A partial differential diagnosis includes the following:

- BV
- Candidiasis
- Trichomoniasis
- PID
- Latex or condom allergy
- Urinary tract infection (UTI)
- Condyloma
- Herpes simplex virus (HSV)
- Contact dermatitis (e.g., from irritants, perfumes)
- Chlamydia
- Gonorrhea
- Normal vaginal discharge

## P: Plan

### Diagnostic Evaluation

- Obtain a cervical sample for STD testing, if indicated.
- Obtain samples (swabs) from the vaginal wall for wet mounts and pH testing.
- Wet mounts: Perform microscopic examination of saline and potassium hydroxide (KOH) preparations for the following:
  - WBCs, clue cells, motile trichomonads (saline slide)
  - Yeast forms (KOH)
- Perform a whiff test of KOH preparation; if positive, check pH (if >4.5, likely BV or trichomoniasis).

Treatment depends on the specific diagnosis, and in general is the same as for HIV-uninfected women.

## Trichomoniasis

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis*. Many infected women have a diffuse, malodorous, yellow-green discharge. Most men who are infected with *T. vaginalis* have no symptoms; others have symptoms of nongonococcal urethritis. The diagnosis usually is made by visualization of motile trichomonads on microscopic examination of wet mounts. Antigen or nucleic acid assays have greater specificity and sensitivity than wet mount preparations, and may be used if microscopy is negative. Culture of vaginal secretions is the most sensitive and specific diagnostic test for *T. vaginalis*, and also may help to rule out other infections.

### Treatment: Recommended regimen

- Metronidazole 2 g PO in a single dose
- Tinidazole 2 g PO in a single dose

### Treatment: Alternative regimen

- Metronidazole 500 mg PO BID for 7 days

### Treatment during pregnancy

- Metronidazole, as in nonpregnant women (see above); the 7-day regimen may be better tolerated.
- Counsel patients about the potential risks and benefits of therapy. In pregnant women with asymptomatic trichomoniasis, deferring therapy until after 37 weeks' gestation may be considered; consult with a specialist.

### Treatment notes:

- Single-dose metronidazole is associated with more side effects than the other treatment regimens.
- Sex partners should be treated. Patients should refrain from unprotected intercourse until both partners have resolution of symptoms and have completed treatment; this should be at least 7 days after single-dose therapy.

- Patients must avoid alcohol while taking metronidazole or tinidazole, and for at least 1 day after discontinuing metronidazole and 3 days after discontinuing tinidazole. The combination of alcohol and these drugs may cause a disulfiram-like reaction. Patients taking ritonavir capsules or tipranavir also may experience symptoms because of the small amount of alcohol in the capsules.

#### Treatment failure

Certain strains of *T. vaginalis* have diminished susceptibility to metronidazole and must be treated with higher dosages. If treatment failure occurs on metronidazole, consider tinidazole as above, or if single-dose metronidazole was used initially, consider metronidazole 500 mg PO BID for 7 days. If this is not effective, consult with a specialist.

#### Bacterial Vaginosis

BV is a clinical syndrome resulting from loss of the normal vaginal flora, particularly *Lactobacillus*, and replacement with anaerobic and other bacteria such as *Gardnerella vaginalis* and *Mycoplasma hominis*. The diagnosis is made on clinical and laboratory criteria. Usually, three of the following four characteristics should be present (note: only the clue cells are specific to BV):

- Homogeneous, gray-white, noninflammatory discharge on the vaginal walls
- Clue cells on the wet-mount slide
- Vaginal fluid pH level of >4.5
- Fishy odor to the vaginal discharge before or after the addition of KOH (whiff test)

Vaginal culture does not help establish the diagnosis. Rapid diagnostic test cards are available in some settings.

Many studies have documented an association between BV and infections such as endometritis, PID, and vaginal cuff cellulitis after gynecologic procedures. Therefore, the U.S. Centers for Disease Control and

Prevention (CDC) recommends screening for and treating BV before invasive gynecologic procedures.

The sex partners of women with BV do not need to be treated.

#### Treatment: Recommended regimens

- Metronidazole 500 mg PO BID for 7 days
- Metronidazole gel 0.75%, 1 full applicator (5 g) intravaginally QHS for 5 days
- Clindamycin cream 2%, 1 full applicator (5 g) intravaginally QHS for 7 days

#### Treatment: Alternative regimens

- Tinidazole 2 g PO QD for 2 days
- Tinidazole 1 g PO QD for 5 days
- Clindamycin 300 mg PO BID for 7 days
- Clindamycin ovules 100 g intravaginally QHS for 3 days

#### Treatment during pregnancy

- Symptomatic pregnant women should be treated with oral metronidazole (500 mg BID or 250 mg TID) or oral clindamycin 300 mg BID for 7 days.

#### Treatment notes:

- Patients must avoid alcohol while taking metronidazole or tinidazole, and for at least 1 day after discontinuing metronidazole and 3 days after discontinuing tinidazole. The combination of alcohol and these drugs may cause a disulfiram-like reaction. Patients taking ritonavir capsules or tipranavir also may experience symptoms because of the small amount of alcohol in the capsules.

#### Treatment failure

Consider re-treatment for 7 days with metronidazole or clindamycin. Consider the possibility of an alternative or second cause of the patient's symptoms, as multiple conditions or pathogens may present concurrently. Perform testing for other conditions as

suggested by symptoms, or if symptoms do not resolve with initial treatment:

- Perform herpes culture if indicated by lesions; see chapter *Herpes Simplex, Mucocutaneous*.
- Test for chlamydia and gonorrhea if indicated; see chapter *Gonorrhea and Chlamydia*.
- Perform urinalysis (with or without culture and sensitivities) if urinary symptoms are prominent.
- If an irritant or allergen is suspected, including N-9, discontinue use.
- If symptoms are related to the use of latex condoms, switch to polyurethane male or female condoms.
- For tenderness on cervical motion or other symptoms of PID, see chapter *Pelvic Inflammatory Disease*.
- Perform workup or obtain referral as needed for other abnormalities found on bimanual examination.

For information on other STDs or related conditions, see the CDC treatment guidelines at [www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment).

## Patient Education

- Advise patients to avoid any form of alcohol while taking metronidazole or tinidazole and for 24 hours after taking the last dose (72 hours after the last tinidazole dose). Alcohol and metronidazole together can cause severe nausea, vomiting, and other immobilizing symptoms.
- Patients taking ritonavir capsules may experience these symptoms because of the small amount of alcohol in the capsules and should be told to contact their health care provider if nausea and vomiting occur.

- Advise patients that clindamycin cream and ovules are oil based and will weaken latex condoms, diaphragms, and cervical caps. Patients should use alternative methods to prevent pregnancy and HIV transmission.
- Recurrence of BV is common. Patients should contact their health care provider and return for repeat treatment if symptoms recur.
- Instruct patients to avoid douching.
- To avoid being reinfected by *Trichomonas*, patients should bring their sex partners to the clinic for evaluation and treatment.

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