Chapter 8:

Symptom Management

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Workup of Symptoms

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

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

Medication-related Issues

What are the most common symptoms related to antiretroviral medications?

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

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

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

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

Symptoms of life-threatening acute drug reactions are not to be missed. A patient with myalgias, nausea, vomiting, diarrhea, abdominal pain, fever, rash, malaise, and extreme fatigue who has started taking abacavir (ABC) within the previous 6 weeks is probably suffering from an abacavir hypersensitivity reaction. In this case, abacavir should be permanently discontinued. The hypersensitivity reaction occurs in up to 5% of patients starting on abacavir and can lead to hypotension and death if the patient is rechallenged with abacavir. If a patient taking one of the "d-drugs" (didanosine [ddI], zalcitabine [ddC], stavudine [d4T], dapsone [for *Pneumocystis* pneumonia prophylaxis]) has rapid onset of nausea/vomiting and constant, severe abdominal pain in the epigastrium or upper quadrants that radiates to the back, drug-induced pancreatitis is possible. Patients taking a nucleoside (NRTI) who have vague symptoms including nausea, vomiting, abdominal pain, weight loss, malaise, fatigue, dyspnea, or fever must have lactic acidosis with hepatic steatosis ruled out. This occurs 5-13 months after initiating therapy and has a 60% fatality rate. Patients taking nevirapine (NVP) who have fatigue, malaise, nausea, vomiting, jaundice, and right-upper-quadrant abdominal pain could have nevirapine-induced hepatitis. Also, up to half the patients taking nevirapine may have a rash; however, if the rash is moist, involves the mucous membranes, or is extensive with an associated fever, Stevens-Johnson syndrome, which also occurs in patients taking trimethoprim-sulfamethoxazole (TMP/sulfa), must be considered. Severe cases of Stevens-Johnson syndrome, including toxic epidermal necrolysis (TEN), are medical emergencies and must be managed as burn cases. For all drug-induced, life-threatening illnesses, immediate discontinuation of the offending drug is the crucial first step in care.

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

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

Table 8-1. Side Effects of Antiretroviral Drugs

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

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

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

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

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

NAUSEA

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

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

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

What are the best options for managing nausea?

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

Pulmonary Symptoms

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

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

What workup is appropriate?

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

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

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

How common is sinus disease in patients with HIV?

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

FATIGUE

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

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

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

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

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

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

NEUROPATHIC PAIN

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

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

How do you diagnose and treat DSP?

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

Dermatologic Symptoms

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

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

Table 8-4. Common Causes of Pruritus in Patients with HIV

Very common	Less common
• *Staphylococcal folliculitis* • *Xerosis* • *Atopic dermatitis* • *Scabies* • *Psoriasis* • *Hypersensitivity to insect bites* • *Drug reactions*	• *HIV-associated pruritus* • *Eosinophilic folliculitis* • *Granuloma annulare* • *Lymphoma* • *Hepatic failure* • *Renal failure*

How does scabies manifest differently in HIV-infected persons?

Among HIV-infected persons with mild-to-moderate immune suppression, scabies causes similar clinical manifestations as seen in persons without HIV infection, namely multiple pruritic papular lesions. Treatment consists of applying 30-60 g of 5% permethrin cream to the entire body from the neck down, leaving it on for 8-12 hours, then washing it off, and repeating the entire process one week later. In HIV-infected persons with severe immune suppression (CD4 count of < 100 cells/mm^3), an atypical form of scabies known as crusted or "Norwegian" scabies may develop. Crusted scabies is characterized by an enormous number of scabies mites and manifests as nonpruritic, thick, grayish-white, plaque-like lesions. In severe cases, the large lesions can develop deep fissures. Treatment of crusted scabies consists of ivermectin 200µg/kg orally with a repeat dose a week later.

Table 8-5. Therapy Strategies and Treatment Options for Generalized Pruritus

Therapy	Comment
Prevention of scratching	Scratching causes secondary irritation
Lubrication with ointments and creams with a fatty basis	eg, propylene glycol, wax esters
Avoidance of histamine induction by heat	eg, bathing in lukewarm or cold water
Avoidance of irritating substances	eg, alkaline soaps, wool clothing
Antihistamines	The evidence is sparse; watch for side effects
Topical agents • *Coolants* • *Anesthetic agents*	 *eg, menthol, phenol* *eg, EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%)*
Lindane	Empiric treatment for scabies if risk factors
UVB therapy	Three times a week, up to 20 treatments for maximal benefit
Hypnosis	Studies have demonstrated benefit

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

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

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

Among HIV-infected persons with mild or moderate immune suppression (CD4 count > 350 cells/mm^3), herpes simplex virus (HSV) infections cause clinical manifestations similar to those in HIV-negative persons, namely self-limited oral or genital lesions that typically appear with vesicular or ulcerated lesions. Recommended therapy for episodic HSV infection consists of either acyclovir 400 mg po tid x 5-10 days, famciclovir 500 mg po bid x 5-10 days, or valacyclovir 1000 mg po bid x 5-10 days. In persons with more advanced immune suppression, particularly those with severe immune suppression (CD4 count < 100 cells/mm^3), HSV infection may present as a non-healing, large, ulcerated lesion anywhere on the body. Therapy for these chronic, ulcerated lesions typically requires longer duration. In addition, those HIV-infected persons with severe immune suppression who receive chronic suppressive therapy for HSV have an increased risk of developing acyclovir-resistant HSV infection.

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

Among HIV-infected patients with severe immune suppression (CD4 count < 100 cells/mm^3), molluscum contagiosum typically presents as flesh-colored, papular lesions, most often on the face, neck, chest, or genitalia. In contrast to immune competent patients who typically have a self-resolving illness, HIV-infected persons with severe immune suppression generally have a progressive increase in the number and size of the molluscum lesions, often culminating in very large and disfiguring lesions referred to as "giant molluscum." These lesions are particularly problematic if located on the face. Extremely large lesions may require surgical removal, moderate-sized lesions typically respond to liquid nitrogen therapy, and multiple small lesions are best treated with topical tretinoin 0.025% applied once a day. In addition, effective ART with improvement in immune function may help in managing molluscum.

How do you recognize and treat seborrheic dermatitis?

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

Mouth Lesions

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

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

Mucosal *candida* infections are seen as the CD4 cell count falls below 200-300 cells/mm^3. The manifestations vary; they can involve the hard and soft palates, buccal mucosa, tongue, pharynx, and hypopharynx. The most common presentation is pseudomembranous candidiasis, or thrush. "Cottage cheese" plaques are seen on the soft palate, tonsils, and buccal mucosa and can be removed with a tongue blade. Atrophic candidiasis is a less seen and underdiagnosed form of candidiasis, consisting of flat, erythematous plaques in the same distribution as pseudomembranous candidiasis but lacking the white exudates. Mouth pain and loss of acuity of taste are common symptoms with atrophic candidiasis.

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

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

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

How do you recognize and treat gingivitis and periodontal disease?

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

WASTING

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

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

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

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

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

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

mass can be measured using mid-arm circumference. Specific dietary deficiencies should be addressed, vitamin and mineral supplements should be prescribed, and high-calorie protein-containing foods should be recommended. In the patient with a low CD4 count (< 100 cells/mm^3), OIs such as *Mycobacterium avium* complex (MAC), tuberculosis, cytomegalovirus infection, cryptosporidiosis, and *Pneumocystis carinii* pneumonia (PCP) should be ruled out, as well as lymphoma. Order a complete blood count, chemistries, blood cultures, chest x-ray, oximetry, and gastrointestinal biopsies or stool cultures as indicated. Referral to a nutritionist or registered dietician is often helpful. Also see *Health Care and HIV: Nutritional Guide for Providers and Clients* under Suggested Resources for practical assessment tools and algorithms for providers as well as patient handouts.

What are the medical treatment options for AIDS wasting?

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

MYALGIAS

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

HIV can cause an inflammatory myopathy at any stage of infection. Symptoms include slowly progressive, proximal muscle weakness of the extremities with or without myalgias. Myopathy due to zidovudine (AZT) toxicity presents similarly to HIV-associated myopathy, and it may be difficult to distinguish between these two disorders. Zidovudine toxicity occurs usually after several months of therapy (most commonly after 6 or more months of continual therapy). Myopathy or rhabdomyolysis due to HMG coenzyme A reductase inhibitors (statins) or fibrates are another important concern with HIV-infected patients. Many patients are on these drugs for treatment of hyperlipidemia caused by treatment with PIs. PIs decrease the metabolism of statins, which can increase the chance of toxicity. Moreover, many patients are on both gemfibrozil and a statin, which can interact to increase the risk of muscle toxicity. Simple myalgias are more common than rhabdomyolysis or myopathy caused by the statins.

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

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

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

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

DIARRHEA

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

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

Table 8-8. Infectious Causes of Diarrhea in Patients with HIV

Any CD4 cell count (acute diarrhea)
Viruses (especially Norwalk virus)
Clostridium difficile (previous antibiotic exposure)
Salmonella spp
Shigella spp
Campylobacter spp
Any CD4 cell count (chronic diarrhea)
Clostridium difficile
Giardia lamblia
CD4 count <300 cells/mm^3 (chronic diarrhea)
Microsporidia
Cryptosporidia
Mycobacterium avium complex (CD4<100)
Isospora belli
Cytomegalovirus (CD4 count <100/mm^3)
Idiopathic

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

For patients who are on medication that can cause intractable diarrhea, one option is a trial of antidiarrheal medications (loperamide or atropine/phenoxylate either alone or in combination) and continuation of the previous antiretroviral regimen. If this does not work, another option is a trial off medication. If a patient is on ART, stop all medications for the 1-week evaluation period. If there is a response, then a new agent can be substituted for the most likely causative drug, usually nelfinavir (NFV) or lopinavir plus ritonavir (LPV/r, or Kaletra). If there is no response when medications are stopped, then stool studies should be done. If the patient has a high CD4 cell count (> 300/mm^3), start with *C. difficile* toxin and *Giardia* antigen. If the CD4 cell count is low (< 300/mm^3), do a full workup with *C. difficile*, *Giardia* antigen, *Microsporidia/Cryptosporidia* assay, and modified AFB stain for cryptosporidia. If no organisms are identified, in patients with very low CD4 cell counts (< 100/mm^3) obtain blood cultures for *Mycobacterium avium*, and if these are negative, pursue lower endoscopy with particular emphasis on detection of cytomegalovirus on biopsy. In patients with higher CD4 cell counts, clinical followup and trials of antimotility drugs are a reasonable approach before pursuing endoscopy.

HEADACHE

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

The causes of headache vary according to CD4 cell count. Patients with a CD4 count of > 300 cells/mm^3 usually have headaches with common causes such as muscle tension, migraine, or drug side effect. Sinusitis is more frequent in patients with than without HIV and may cause headaches. In patients with low CD4 counts (< 200 cells/mm^3) opportunistic infections (eg, Cryptococcal meningitis, toxoplasmic encephalitis) and malignancies (eg, CNS lymphoma) are important causes to consider.

How should you work up patients with headache?

Patients with CD4 counts of < 200 cells/mm^3 should have a contrast head CT scan or MRI, followed by lumbar puncture if the scan does not reveal a cause. In a study of CT scans for evaluation of headaches in HIV-positive patients *all* cases with mass lesions or white-matter lesions occurred in patients with CD4 counts of < 200 cells/mm^3. Serologic tests for cryptococcal antigen and *Toxoplasma* titers are helpful in patients with CD4 counts of < 200 cells/mm^3.

KEY POINTS

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

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

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

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

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

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

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

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

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

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

Headaches, common with HIV disease, may be due to a CNS infection or neoplasm if the CD4 count is less than 200 cells/mm^3.

SUGGESTED RESOURCES

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CASES

1.

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

Question: What is the most likely diagnosis?

Answer:

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

Question: What is the most likely cause?

Answer:

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

2.

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

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

Answer:

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

Question: What initial lab work should be ordered?

Answer:

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