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CHAPTER 23

Gastrointestinal Disorders in HIV

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Introduction

Gastrointestinal disease in human immunodeficiency virus (HIV) spans the entire GI tract from the mouth to the rectum. The spectrum of gastrointestinal symptoms in HIV ranges from odynophagia and dysphagia, to nausea and vomiting, to abdominal pain and finally diarrhea and tenesmus. As with normal hosts, gastrointestinal disorders are very common in HIV patients, whether it be from opportunistic infections secondary to the patient's immunosuppressed status, medication induced, or through other etiologies. Almost all HIV and AIDS patients have some gastrointestinal complaints throughout the course of their illness. With the dramatic changes in HIV care because of highly active antiretroviral therapy (ART) in the mid-1990s, the incidence of opportunistic infections are decreasing, and as a result, the clinical picture of gastrointestinal illnesses in HIV is changing. The evaluation of the HIV patient with gastrointestinal complaints requires a thorough history and physical exam, in addition to selected studies, in order to diagnose the correct disease and treat accordingly.

Esophageal Disorders

Patients with HIV and AIDS typically can have upper gastrointestinal symptoms, which can range from dysphagia, or difficulty swallowing, to odynophagia, or the feeling of pain upon swallowing. At least one-third of patients with HIV before the ART era had esophageal complaints,[1] and the incidence increased with the progression of the disease. Most of the symptoms in these patients are secondary to opportunistic infections caused by the patient's immunosuppressed state, and related to the degree of immunosuppression. The most common etiologies of esophageal pathology and esophagitis in AIDS patients (Table 23.1) are *Candida* species, herpes simplex virus (HSV), and cytomegalovirus (CMV).[2] In addition, there is also an entity of idiopathic esophageal ulcers (IEU) that is also seen in HIV patients, which may be immunologically mediated,[3] or caused by HIV itself.[4] Other etiologies of esophageal complaints include malignancy (especially lymphoma and Kaposi's sarcoma) and other non-infectious causes. However, with the introduction of protease inhibitors (PIs) in 1996 and ART, and the decreased incidence of AIDS, more esophageal complaints in HIV these days are related to common etiologies like gastroesophageal reflux disease (GERD) than opportunistic infections.[5]

In addition to the most common symptoms of dysphagia and odynophagia, other symptoms can also suggest esophageal disease in HIV patients, like chest pain, nausea, vomiting, anorexia and weight loss. The symptoms can be acute or have a more chronic, progressive course. In addition, dysphagia is often associated with candidal esophagitis, whereas odynophagia is generally symptomatic of esophageal ulcerative disease. Patients can have both dysphagia and odynophagia, and because they also may have more than one illness concurrently, it is

Table 23.1 Esophageal diseases in HIV patients

Etiology	Symptoms	Diagnosis	Endoscopic appearance	Treatment
Candida	Dysphagia Odynophagia	Response to empiric fluconazole. Endoscopy	Creamy whitish-yellow adherent plaques 'shaggy appearance'	Fluconazole 200 mg p.o., then 100 mg p.o. q.d. Clotrimazole troches. Amphotericin B i.v. 0.3– 0.5 mg/kg per day. Caspofungin i.v. 70 mg × 1; 50 mg/day
CMV	Odynophagia Dysphagia	Endoscopy with biopsy (inclusions on pathology)	Single or multiple ulcers; giant ulcers; diffuse esophagitis	Ganciclovir i.v. 5– 10 mg/kg per day. Foscarnet i.v. 90 mg/kg b.i.d. Valganciclovir p.o. 900 mg/day. Cidofovir 5 mg/kg weekly.
HSV	Odynophagia Dysphagia Chest pain Nausea/vomiting	Endoscopy with biopsy (from ulcer edge)	Well-circumscribed 'volcano' ulcer; 1–3 mm vesicles	Acyclovir p.o./i.v. 15– 30 mg/kg per day. Valacyclovir p.o. 1 g b.i.d. Famciclovir 500 mg b.i.d. Foscarnet i.v. 40 mg/kg b.i.d.
Idiopathic esophageal ulcers (IEU)	Odynophagia	Endoscopy with biopsy. Diagnosis of exclusion	Variable	Prednisone p.o. 40 mg/day. Thalidomide p.o. 200 mg/day.
GERD	Dyspepsia Belching Nocturnal cough	Endoscopy. Therapeutic and behavioral management	Esophagitis. Hiatal hernia	Oral H_2 blockers. Oral proton pump inhibitors. Behavioral modifications.
Malignancy (Kaposi's sarcoma and lymphoma most common)	Dysphagia Weight loss Hematemesis	Endoscopy with biopsy. Radiology (CT scan)	Variable. Neoplastic mass	Antiretroviral therapy. Surgery. Chemotherapy. Radiation.
Pill-esophagitis	Dyspepsia odynophagia	History Endoscopy	Variable ulcerations	Behavior or pharmaceutical modification.

CMV, cytomegalovirus; HSV, herpes simplex virus; GERD, gastroesophageal reflux disease; H_2, histamine-2. Adapted with permission from Sande MA, Volberding PA, eds. Medical Management of AIDS, 6th edn. Philadelphia: WB Saunders.

imperative to pursue a thorough investigation as to the etiology of esophageal complaints in HIV patients.

The evaluation of HIV patients with esophageal symptoms does not definitively need to include endoscopy with biopsy, but this is the gold standard, as it allows the physician to visualize the esophageal lumen, and to biopsy affected sites (Fig. 23.1). The history and physical exam is obviously important, as it may lead to a discovery of GERD, or pill-induced esophagitis. In addition, patients with disseminated CMV (e.g. CMV retinitis) with esophageal symptoms (especially odynophagia) may respond to CMV antiviral therapy in the absence of diagnostic endoscopy and biopsy. The most common sign on physical exam that relates to esophageal complaints is oral thrush, which can be suggestive of esophageal candidiasis in patients with esophageal complaints. In these patients, especially those with only dysphagia (or dysphagia and odynophagia, but not those with solely odynophagia) it may be beneficial to document the response from an empiric trial of oral fluconazole, as opposed to endoscopy.[6] If there is a symptomatic response to the fluconazole, then it can be presumed the patient had candidal esophagitis and proceed accordingly.

In addition to history and physical exam, there are other ways to evaluate esophageal complaints. Barium esophagography is relatively insensitive and non-specific and should not be used for diagnostic

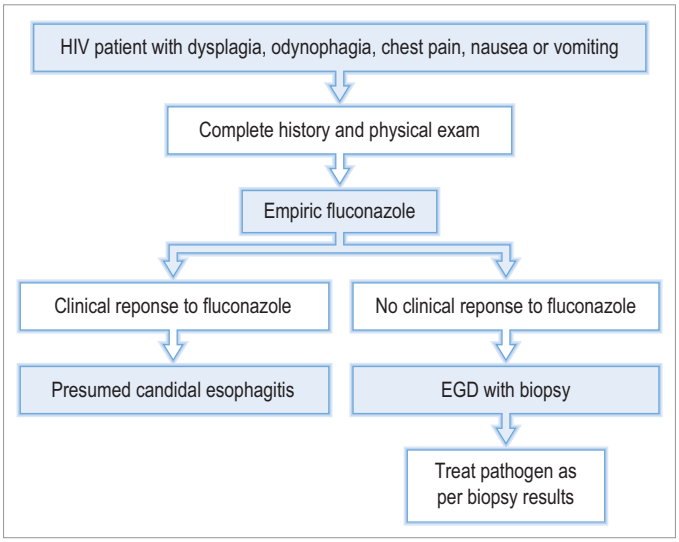

Figure 23.1 Algorithm in the approach to the HIV patient with esophageal complaints.

purposes, but the most characteristic finding in candidal esophagitis is diffuse mucosal irregularity resulting in a 'shaggy' appearance mimicking diffuse ulceration.[7] CMV and IEU may appear as well circumscribed ulcers that may be shallow or deep, and are indistinguishable on barium swallow.[8] Of course, radiography can determine a neoplastic origin to dysphagia in patients with malignancies. Another form of evaluation is brush cytology, where a cytology brush is passed through a nasogastric tube and obtains tissue for viral cultures and immunohistochemistry. Unfortunately, this leads to large sampling error, because it is done blindly without visualization of the lumen, and misses diagnoses (as patients may have two infectious processes, and IEU cannot be diagnosed). Viral culture and cytologic brushings add little in the evaluation of AIDS patients with esophagitis over endoscopy with biopsy.[9] Endoscopy with biopsy generally yields a viral or fungal diagnosis based on culture and hematoxylin and eosin staining (which will exclude a viral etiology); only after several biopsy samples do not show any etiology of the ulcerations can a tentative, exclusionary diagnosis of IEU be made.

Candidal esophagitis is the most common cause of esophagitis in HIV patients, especially in patients with complaints of dysphagia, or odynophagia and dysphagia.[10] The fungal isolate is generally *Candida albicans*, though other species of *Candida* can also affect the esophagus. It should be suspected in patients with a CD4+ lymphocyte count of <100 cells/mm^3 (though can occur at any CD4+ count), and esophageal symptoms with or without thrush, which can be absent in 30% of patients.[11] In patients with HIV and new onset symptoms, an empiric trial of standard dosed fluconazole is an effective strategy, as 82% of patients in a prospective study responded. If there is no response, endoscopy can be pursued.[6] In patients that fail empiric antifungal therapy, the most common etiology (in 77% of the patients) is ulcerative esophagitis as opposed to persistent candidiasis.[12] Fluconazole is the drug of choice for candidiasis, with a loading dose of 200 mg orally followed by 100 mg daily from 10–14 days. Clotrimazole troches are also successful, as topical treatment of esophageal candidiasis,[13] but nystatin is not.[14] Itraconazole and ketoconazole are efficacious systemic therapies, but not as effective as fluconazole.[15,16] Amphotericin B is also a helpful therapy, but is generally used only in azole-resistant patients because of the toxicity of the medication. Low-dose amphotericin (0.3–0.5 mg/kg per day for 7–14 days) is usually adequate. Caspofungin can also be used in candidal esophagitis, and is felt to be as efficacious as fluconazole and well tolerated.[17] However, it is only available in intravenous form and is more expensive, but may be the drug of choice for azole-resistant mucosal candidiasis because of the relative lack of toxicity compared with amphotericin B. Primary prophylaxis of candidal disease is not recommended because of the non-life-threatening nature of the disease, the effectiveness of acute therapy, and the risk of antifungal resistance.

While *Candida* is the most common esophageal pathogen, it can also occur in addition to ulcerative esophagitis in HIV patients. CMV esophagitis is the

most common etiology of odynophagia in HIV patients and therefore esophageal ulcerations, up to 45% of patients in one prospective study.[18] Fever and substernal chest pain can be reported in addition to odynophagia, and thrush can be concomitant, but dysphagia is very uncommon. The diagnosis of CMV is best made by endoscopy and biopsy, with the pathology showing viral cytopathic effect in the gastrointestinal mucosa via intranuclear inclusions. Immunohistochemistry is also helpful for confirmation, as viral cultures are less sensitive and specific.[19]

CMV is the most common viral pathogen in the esophagus in HIV patients, and esophagitis is the most common extraocular manifestation of CMV.[20] It can appear as a diffuse esophagitis, single or multiple ulcers, or giant ulcers involving the whole esophagus, and generally occurs when the CD4+ lymphocyte count is <50. It may be discovered only after treatment for *Candida*, as they may exist concurrently in 20% of patients.[21] The incidence of CMV esophagitis has declined dramatically in the ART era. Treatment for CMV esophagitis involves a wide array of antiviral medications, namely ganciclovir, valganciclovir, foscarnet, and cidofovir. Ganciclovir was the first agent used to combat CMV and has the most data behind it; the response rate is about 70–80%. It is given intravenously in a 2–4 week induction period, 5–10 mg/kg per day, but has dose limiting side-effects, mainly bone marrow suppression (and resultant neutropenia and thrombocytopenia). Oral ganciclovir can also be used as maintenance therapy, but the data is limited. Intravenous foscarnet (90 mg/kg b.i.d., 2–3 weeks) is seen as equally effective to intravenous ganciclovir in the treatment of CMV esophagitis, but comes with a nephrotoxic side-effect profile; however, randomized studies have shown equal efficacy and safety.[22] Foscarnet is generally used in cases of clinical failure after ganciclovir induction.[23] Oral valganciclovir (900 mg/day) has not been tested in CMV esophagitis, but does have 60% of the bioavailability of intravenous ganciclovir. Cidofovir also can treat CMV, but is not typically used because of nephrotoxicity.

HSV esophagitis is a relatively uncommon cause of esophageal ulceration in HIV patients compared with CMV and IEU. The endoscopic appearance is described as being well circumscribed and having a 'volcano' like appearance, distinguishing them from the ulcers seen in CMV infection, which tend to be linear or longitudinal and are deeper.[24] Treatment is with oral acyclovir (15–30 mg/kg per day), though if patients have difficulty with swallowing, intravenous acyclovir can be used. Valacyclovir and famciclovir can also be used because of their efficacy and convenient dosing schedules. Foscarnet intravenously (40 mg/kg b.i.d.) is used in cases of acyclovir resistance.[25] Secondary prophylaxis with valacyclovir (500–1000 mg/day) is recommended in patients with frequent relapses.

Idiopathic esophageal ulcers (IEU) are a diagnosis of exclusion if none of the pathologic, fungal, or viral studies return a diagnosis. The treatment of idiopathic esophageal ulcers is done with oral corticosteroids, generally starting at 40 mg of oral prednisone daily.[26] If the patient cannot take medications orally, then the corticosteroids can be given intravenously. In addition, thalidomide can also be used for IEU if corticosteroids are not efficacious.[27]

In addition to the infections and ulcerations discussed above, there are other esophageal issues in HIV, namely motility and neuropathic issues. There is a form of HIV neuropathy that could lead to gastrointestinal complaints, like gastroparesis. These would be treated symptomatically, with prokinetic agents like metoclopramide. Additionally, in patients with both symptomatic esophageal complaints, as well as those that are asymptomatic, there are findings of esophageal motility abnormalities. This is probably because of the neurotropic nature of HIV leading to autonomic dysfunction in the gastrointestinal neurologic plexus.[2]

Gastric Disorders

The problems associated with the stomach in HIV patients are similar to the stomach problems of non-HIV infected individuals. Opportunistic infections that affect HIV patients typically do not affect the stomach. Symptoms and presentation are often related to abdominal pain, nausea or vomiting. The most common manifestations of gastric illness in HIV patients is like the general population, namely GERD, peptic ulcer disease (PUD) and gastritis. Care needs to be used when prescribing Histamine-2 (H_2) blockers or proton-pump inhibitors (PPIs), however, as these medications can interact with ART, especially PPIs. Work-up is the same as with the general population, and endoscopy with biopsy is the gold standard for diagnosis. *Helicobacter pylori*, a common cause of peptic ulcer disease in non-HIV positive patients, seems to have a decreased incidence in HIV patients compared with the general population; CMV may actually be the leading cause of PUD in HIV patients.[28] As far as actual HIV-related gastric pathology, gastric lymphoma, Kaposi's sarcoma, and some of the opportunistic organisms (e.g. CMV,

tuberculosis, toxoplasmosis, and cryptococcosis) can be seen. In addition, dyspepsia, nausea and vomiting can all be related to the side-effects of various antiretroviral medications.

Diarrhea

One of the most common complaints of HIV patients is diarrhea. The reasons for diarrhea are multifold, but most commonly relate to opportunistic infection and antiretroviral medications. A more in depth coverage of diarrheal illness in HIV patients is discussed later in Ch. 65: *Etiology and Management of Diarrhea in HIV-infected Patients and Impact on Antiretroviral Therapy*, but an overview will follow here. As with esophageal disease, the incidence of opportunistic infections has decreased in the ART era, though the incidence of chronic diarrhea has remained steady even in the ART era.[29] The evaluation of diarrhea includes a thorough history and physical, as much can be determined from just eliciting the patient's history of symptoms. If the diarrhea occurs with upper abdominal cramps, or bloating, this suggests an upper intestinal source, or enteritis. Bloody diarrhea, tenesmus, and lower abdominal cramping imply colonic involvement. In addition, patients with a history of receptive anal intercourse have a higher involvement of colitis and sexually transmitted pathogens (e.g. gonorrhea, HSV, etc.) in the anorectal area. Homosexual or bisexual men have a 3-fold higher incidence of diarrhea than patients in other risk groups. Obviously, travel and diet history can also be important in the histories of HIV patients with diarrhea. As with other aspects of HIV, opportunistic infections tend to be more common in the setting of lower CD4+ lymphocyte counts (and therefore greater immunosuppression).

The diagnostic studies involved in the work-up of diarrhea in the HIV patient are similar to those in the general population. In addition to history and physical exam (exam specifically adds little to diagnosis, other than evidence of malnutrition), the first route of investigation is often the stool examination. The tests to order include bacterial culture, *clostridium difficile* toxin assay, as well as looking for ova and parasites, especially *Isospora*, *Cryptosporidium*, and *Microsporidia*. These generally need to be specified as potential pathogens when the sample is sent to microbiology when looking at ova and parasites. In addition, a gram stain or methylene blue stain for fecal leukocytes can also be helpful, as evidence of fecal leukocytes may point towards a picture of colitis. Another form of non-invasive testing is blood cultures and serologies, which can be helpful for the diagnosis of systemic opportunistic infections like *Mycobacterium avium intracellulare* (MAI) or viral etiologies like CMV. Especially in the patients who have diarrhea and fever, MAI may be a possibility. However, with all of these etiologies, a diagnosis may be treated, and symptoms may still persist as secondary infections may also be present. For colitis, a barium enema or abdominal radiography may detail the presence of a toxic megacolon, a complication of *Clostridium difficile* colitis.

In addition to the non-invasive studies listed above, in the absence of a diagnosis, the workup for diarrhea should include some invasive studies as well. The first step is generally a flexible sigmoidoscopy, which can give visualization of the colon (to diagnose or rule out pseudomembranous colitis, among other etiologies) and provide tissue for biopsy. Abnormal tissue should be biopsied, but if the mucosa is normal then random tissue can be sent. The flexible sigmoidoscopy is better than the alternatives as it does not require sedation. If small intestinal etiology is suspected, an EGD (going past the second portion of the duodenum) can help determine the cause of the diarrhea through biopsies of the small bowel, sent not only for pathology, but also electron microscopy and culture analysis. If the flexible sigmoidoscopy is non-diagnostic, and there is still no diagnosis from other studies, a colonoscopy can be performed so more biopsies can be done to rule out opportunistic infections, especially in the ileum. This is rarely done, however, and in general, the absence of definitive diagnosis leads to treatment and evaluation (as will be discussed later).

Infections of the Small Intestine (Enteritis)

The symptoms associated with enteritis are typically associated with diarrhea and prolonged malabsorption leading to malnutrition. This is generally because of opportunistic infections, and, similar to other pathologies in HIV patients, the incidence of enteritis has decreased in the highly active antiretroviral therapy (ART) era. The main symptoms of enteritis are copious voluminous diarrhea (>2 L/day) with dehydration and malabsorption, as opposed to colitis, which is a bloody, painful diarrhea. The work-up of enteritis is detailed above, but specifically should include stool studies, and, if non-diagnostic, esophagogastroduodenoscopy (EGD) with biopsy. The etiologies of enteritis in HIV patients are multifold, and include bacterial, viral,

fungal, and parasitic pathogens. These can be diagnosed by the stool studies detailed earlier.

Parasites may be the most common etiology for enteritis, especially in those patients not on ART and greatly immunosuppressed. Parasites are typically diagnosed through stool analysis for ova and parasites, including direct fluorescent antibody (DFA), enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR). Light microscopy can be used, though PCR can be diagnostic at much lower levels of parasitic infection. *Cryptosporidium parvum* is the most commonly identifiable pathogen in AIDS related persistent diarrhea, especially in patients with CD4+ lymphocyte counts <200. It is typically treated with paromomycin 1500–3000 mg every 6–8 h orally, or Azithromycin 900–1200 mg four times a day, though albendazole 400 mg twice a day has also shown to be effective. Nitazoxanide (1 g twice daily for at least 2 weeks) can also be used in the treatment of cryptosporidiosis, but a cure is generally not possible if the CD4+ lymphocyte count is <50. However, a study with children showed no benefit to nitazoxanide at all in HIV+ children (just HIV seronegative ones).[30] Hyperimmune bovine colostrums can also be used, but typically not to cure the parasitic infection.[31]

Microsporidiosis is the next most commonly identifiable refractory diarrhea in HIV patients. This can be treated with albendazole as well (400–1600 mg every 12 h orally) but most cases are poorly responsive to treatment and require indefinite therapy. *Isospora belli* is rare in the USA, but is more common in developing countries. Trimethoprim-sulfamethoxazole, one double strength tablet every 6 h for 10 days is the treatment of choice, but pyrimethamine 50–75 mg four times daily (with folinic acid 5 mg orally four times daily) is acceptable for patients with allergies to sulfa medications.[32] Lastly, *Giardia lamblia* and amoebic dysentery can also occur in HIV patients, at the same incidence as the general population, and can be treated with metronidazole 750 mg thrice daily for 5–10 days, or tinidazole 2 g orally once for giardiasis, 3 days for amebic dysentery.[30] For strongyloidosis, thiabendazole 25 mg/kg twice daily orally is the drug of choice. Albendazole seems to be active against all of the parasitic organisms associated with diarrhea in HIV patients, and could be the first line of therapy when parasitic infection is suspected, pending microbiological study.

With all of the aforementioned parasites, treatment cannot only be targeted at the pathogen, but also at the diarrheal symptoms, with the use of somatostatin analogs like octreotide to try to reduce the amount of diarrhea. In addition, since the parasites are both more common and more chronic at lower CD4+ lymphocyte counts, ART, which reduces the degree of immunosuppression, can also be curative. Opioids such as tincture of opium or codeine can provide symptomatic relief in cases of severe diarrhea through its constipating actions, as well as pain relief.[33] Bulking agents, lactose-free diets, and antidiarrheal medications like diphenoxylate with atropine or loperamide are also beneficial in treating diarrheal symptoms.

Viral infection in HIV patients can cause diarrhea, typically through colitis, but also rarely through an enteritis. CMV, in addition to causing esophagitis, can also affect the GI tract through diarrheal illness, and runs the spectrum from asymptomatic carriage to severe diarrheal illness including appendicitis, bleeding and perforation. It typically occurs in the setting of severe immunosuppression with a CD4+ lymphocyte count <100. The diagnosis of CMV enterocolitis is best made through demonstrating a viral cytopathic effect in tissue specimens, but viral stool cultures can also signify disease (though are less sensitive). The treatment for CMV enterocolitis is mainly ganciclovir and foscarnet, as described earlier in the esophagitis section. Valganciclovir may not achieve adequate bioavailability because of the enterocolitis.

Other viruses can affect the HIV patient gastrointestinal tract, including rotavirus, adenovirus, Norwalk virus, or unusually, picornaviruses, and coronaviruses. These tend to be less common than the other pathologies previously described, and are difficult to diagnose as well. Adenovirus can cause a hemorrhagic colitis; acute diarrhea is seen in patients with only adenovirus in stools, but patients with adenovirus on biopsy specimen generally have a chronic diarrhea.[34] HSV can cause diarrhea via systemic infection in end-stage HIV patients, or can cause a colitis and proctitis through HIV mucosal lesions. HSV can be treated with acyclovir, valacyclovir, famciclovir, or, if acyclovir resistant, foscarnet (as previously described in the esophagitis section).

In addition, HIV itself may be a cause of HIV enteropathy and a diarrheal pathogen, and may be identified in gut tissue in up to 40% of patients, but this is controversial. Idiopathic AIDS enteropathy, on the other hand, is the term used for a chronic diarrhea in an AIDS patient that is without identifiable pathogen or diagnosis (despite intensive investigation). Mucosal hyperproliferation is noted on biopsy. For these etiologies, in addition to ART to increase CD4+ lymphocyte count and reduce immunosuppression, should be treated symptomatically with bulking agents, antidiarrheals, and opioids. The

combination of antidiarrheal therapy with ART has been shown to be more beneficial than antidiarrheal therapy alone in HIV patients with chronic diarrhea.[35]

Other agents that can cause enteritis include *Mycobacterium avium intracellulare* (MAI) and *Pneumocystis jiroveci* (PCP). Small intestinal disease is the most common site of gastrointestinal luminal involvement by MAI.[36] It is often seen with diffuse small bowel infiltration (mimicking Whipple's Disease) and causes severe malabsorption in patients with CD4+ lymphocyte counts of <50. If a malabsorptive diarrhea occurs with fever and night sweats, in addition to weight loss, MAI must be considered, and blood cultures or a bone marrow biopsy may be diagnostic for disseminated MAI infection. Diagnosing MAI enteritis is more difficult, however, as a positive stool is not diagnostic for gastrointestinal disease (though can suggest subsequent disseminated disease).[37] An endoscopic biopsy and acid-fast staining can show acid-fast bacilli and give an ideal diagnosis. Treatment is with a multitude of options, using combinations of clarithromycin 500 mg twice daily, ethambutol 800–1200 mg orally daily, azithromycin 600 mg daily, rifampin 600 mg daily, rifabutin 300 mg daily, amikacin 15 mg/kg three times weekly, and ciprofloxacin 750 mg twice daily. These can reduce, but not eradicate, MAI. Luminal tuberculosis can also occur as an example of extrapulmonary involvement, but is rare; in contrast to MAI, it can generally be treated to cure with antituberculous therapy. *Pneumocystis jiroveci* (PCP) can also be seen as the cause of diarrhea in HIV patients, but is very uncommon, especially in the setting of PCP prophylaxis for AIDS patients; treatment is with antipneumocystis therapy,[38] generally with trimethoprim-sulfamethoxazole.

Colitis

Bacterial infections in HIV patients typically cause a picture of colitis instead of enteritis, with bloody diarrhea and tenesmus. The most common bacterial pathogens seen in HIV patients include salmonellae, Shigella, *E. coli*, *Campylobacter jejuni*, and *Clostridium difficile*. Salmonellosis is 100 times more common in HIV patients than in immunocompetent hosts,[39] and recurrent salmonella bacteremia establishes the diagnosis of AIDS in an HIV patient. The diagnosis is straightforward, as salmonella can normally be cultured in stool specimens in addition to blood culture results. Salmonella gastroenteritis can present with either watery diarrhea or dysentery (mucopurulent diarrhea) with or without fever, abdominal pain, or nausea and vomiting. Though the diarrhea may be self-limited, the treatment is generally ciprofloxacin 500 mg orally twice a day, for 2–4 weeks, for eradication.

Shigella has a similar presentation to salmonellosis, with a similar wide spectrum of presentation of illness. It does come with a high rate of severe complications, including anemia, hypoglycemia, sepsis, hemolytic uremic syndrome, disseminated intravascular coagulopathy and renal failure, with which mortality obviously increases. It also can be treated with ciprofloxacin 500–750 mg twice a day orally for 5–7 days, and is diagnosed by stool culture as well.

Campylobacter jejuni generally presents as a watery diarrhea, and its incidence is probably decreased due to widespread PCP prophylaxis with trimethoprim-sulfamethoxazole. It is typically harder to culture from stool, and may be diagnosed by endoscopic biopsy. Antimicrobial therapy is not essential, though erythromycin 250–500 mg orally four times daily, or ciprofloxacin 500 mg orally twice a day for 5–7 days may reduce the duration of the illness. *E. Coli* may be seen (in any of several strains), and, like the other enteric bacterial diarrheal illnesses, can be treated with a fluoroquinolone like ciprofloxacin. As illustrated, in cases of suspected bacterial diarrhea, ciprofloxacin would cover most enteric pathogens and would be the empiric drug of choice.

Clostridium difficile is seen in HIV patients not only in the presence of antibiotic therapy, but also in the absence of recent antibiotic therapy. The most common antibiotics that cause *C. difficile* are clindamycin, ampicillin, cephalosporins and aminoglycosides. The clinical presentations and response to therapy are not different in HIV patients than in patients without HIV. Diagnosis is made by detecting *C. difficile* toxin in stool assay, and treatment is with metronidazole 250–500 mg orally every 6–8 h for 10–14 days, or tinidazole, in addition to stopping the offending initial antibiotic therapy. In resistant cases, oral vancomycin 250 mg every 6 h can be used, as can rifaximin 200 mg three times daily, though it is not as effective as vancomycin. In cases of suspected *C. difficile* without diagnosis via stool toxin assay, a flexible sigmoidoscopy can look for pseudomembranous colitis, which can be diagnostic for *C. difficile*.

Fungal etiologies of diarrhea in HIV patients are relatively rare, but can occur in patients with immunocompromised states and low CD4+ lymphocyte counts. Gastrointestinal histoplasmosis appears to be the most commonly described fungal etiology of diarrhea in HIV patients, and typically occurs in the

setting of a systemic infection. Diagnosis is made by fungal culture and smear of tissue or blood,[40] and treatment is with amphotericin B 0.5–1 mg/kg per day intravenously initially, with maintenance therapy with itraconazole 200 mg orally daily. Coccidiomycosis and cryptococcosis are also rare, and occur in the presence of systemic infections as well. In addition, as candidal infections are the most common opportunistic infections of HIV patients, a dehydrating diarrhea can also occur as a manifestation of the infection.

Obviously, not all causes of diarrhea in HIV patients are secondary to opportunistic infections. Several noninfectious etiologies of diarrhea in HIV patients can occur as well, including the most common, drug-induced diarrhea. The most common drugs that cause diarrhea in HIV patients are nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs). With protease inhibitors, diarrhea is the most common side-effect reported with nelfinavir and saquinavir, most commonly occurs at the initiation of treatment, and is a cause of cessation of therapy and lack of adherence to treatment.[41] Newer agents like lopinavir-ritonavir seem to cause less diarrhea than older PIs like nelfinavir.[42] Treatment is generally guided towards treatment of symptoms, namely with bulking agents or antidiarrheals like loperamide.

Other causes of diarrhea in HIV patients include inflammatory bowel disease, including Crohn's disease and ulcerative colitis, neither of which have increased incidence in HIV patients. Treatment is tailored according to the disease process itself, though an active disease process may decrease CD4+ lymphocyte count; this may be reversed by colectomy.[43] In addition, AIDS related illnesses that are noninfectious but can also cause diarrhea and gastrointestinal issues include lymphoma and Kaposi's sarcoma, both of which are diagnosed by biopsy. Infiltration of the mucosal tract by the neoplasm can lead to diarrhea and weight loss.

Anorectal Disease

Anorectal disease is a big component of HIV gastrointestinal care, especially among homosexual males. Interestingly, the incidence of anorectal pathology in HIV patients has not been affected by ART.[44] Many anorectal pathologies are seen in HIV patients, including anal fistulas and fissures, perirectal abscesses, ulcerations and proctitis (Box 23.1). In addition, anal neoplasms as a result of human papillomavirus (HPV) and other etiologies can also occur. Anorectal carcinoma has an increased incidence in both HIV patients and among homosexual males, and is the fourth most common malignancy seen in HIV;[45] HIV+ homosexual men have twice the incidence than HIV negative homosexual men. Anal squamous cell carcinoma is frequently associated with squamous intraepithelial neoplasia and HPV, much like cervical carcinoma, and can be detected by anorectal cytology, similar to Papanicolaou smears.[46] The gold standard for diagnosis of anorectal neoplastic disease is still anoscopy with biopsy, though anorectal cytology can be useful as a screening test.

In addition to anal carcinoma, other anorectal symptoms are common in the HIV population, especially among homosexual males. Anal condyloma is the most common HIV related anal pathology, and is associated with HPV infection; treatment options include a variety of surgical options, including cryotherapy. The four most common infectious causes of proctitis in men who have sex with men are gonorrhea, herpes simplex, chlamydia and syphilis.[47] Gonorrhea and chlamydia are typically treated together with ceftriaxone 125 mg i.m. once and azithromycin 1 g orally once; fluoroquinolones, oral cephalospo-

Box 23.1

Differential diagnosis in anorectal disease in HIV patients

Bacterial

- *Neisseria gonorrhea*
- *Chlamydia trachomatis* (including Lymphogranuloma venereum)
- *Treponema pallidum* (syphilis)
- *Shigella*
- *Salmonella*
- *E. coli*

Viral

- Herpes Simplex (HSV)
- Human Papillomavirus (HPV)
- Cytomegalovirus (CMV)

Other

- Anorectal carcinoma
- Crohn's disease
- Ulcerative colitis
- Radiation proctitis
- Anal fissures
- Anal fistulas
- Perirectal abscess.

rins and doxycycline (100 mg orally twice a day for 7 days) can also be used. Primary syphilis is treated with benzathine penicillin G 2.4 million units i.m. once (or doxycycline 100 mg twice daily for 2 weeks if penicillin allergic). HSV infections, as described earlier with esophagitis and colitis, can also cause perianal and rectal ulcerations, with associated symptoms of tenesmus, pain, and bleeding. Treatment is with antiherpetic medications like acyclovir, valacyclovir, or famciclovir, as explained earlier, with foscarnet in acyclovir-resistant cases. Other etiologies of proctitis include lymphogranuloma venereum, as well as other causes of colitis detailed above; clinical overlap can also happen in HIV patients. In addition to a thorough physical examination, all patients with anorectal symptoms should have anoscopy and sigmoidoscopy with mucosal biopsy to look for fissures, perirectal abscesses, and fistulas in addition to searching for opportunistic infections, with microbiological studies sent for viral, fungal and bacterial cultures.

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