Gastrointestinal System and PWH

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HIVC

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Oral Lesions

- Oral Candidiasis (thrush) manifests in a majority of patients with advanced HIV. Lesions usually present when the CD4 count is less than 200/mm^3. The lesion presents with oral pain, ageusia and dysphagia. The creamy white lesions are located on the tongue surface and on the buccal mucosa. Occasionally, it may be asymptomatic. Diagnosis is reached by clinical examination and demonstration of yeast forms and pseudohyphae on potassium hydroxide (KOH) preparation. Culture of the scrapping will be useful in identifying the species of the yeast responsible for the infection. Painful oral lesions are caused by Herpes simplex virus (HSV). They show common vesicles that breakdown to form ulcers and have a tendency to be severe and remain for a longer duration in patients with advanced HIV as compared with the normal population. Currently, viral cultures, HSV DNA polymerase chain reactions and HSV serological antigen studies are strongly recommended to ascertain the diagnosis in HIV-positive patients. Lesions usually respond to oral acyclovir, famciclovir or valacyclovir prescribed over a period of 5–10 days. Intravenous acyclovir is however recommended for severe mucocutaneous herpes infection. Acyclovir-resistant strains, as evident by failure of response within 7–10 days, should be managed with foscarnet, which is the drug of choice.

Esophageal Lesions

- Patients with these lesions present with dysphagia, odynophagia or both. Esophagitis is common in advanced disease; at least one-third of the patients will suffer from eosophageal disease. Patients with eosophagitis are usually symptomatic. Candidal eosophagitis is the most frequent, occurring either alone or in association with other opportunistic pathogens, namely Cytomegalovirus (CMV), HSV and ***Mycobacterium avium intercellulare*** (MAI). CMV and Candida coexist in up to 20% of the patients with eosophagitis. The most common viral pathogen causing eosophageal disease is CMV, identified in 10–40% of endoscopic biopsies of eosophageal lesions. Others occurring less commonly are Epstein-Barr virus, HSV and Papovavirus and human Herpes virus 6 (HHV-6). MAI causes direct eosophageal infection. Rarely, protozoal causes of eosophagitis include ***Cryptosporidium parvum***, Leishmania spp and ***Pneumocystis jirovecii/carinii***, a fungal species, formerly classified among protozoa. Candidal and HSV eosophagitis are predominantly documented in patients with CD4 counts less than 200/mm^3 whereas CMV is almost exclusively seen with CD4 counts below 100/mm^3. In the assessment of the condition, double-contrast barium swallow may show multiple filling defects but endoscopy with biopsy is the best method of diagnosis. Given the preponderance of Candidal infection and the classic examination findings, empirical treatment with either oral fluconazole or itraconazole is indicated. Both have a superior efficacy over ketoconazole. A randomized trial demonstrated endoscopic cure rates of 91% vs 52% for fluconazole and ketonazole, respectively. In addition, increasing the doses of micafungin are as effective as fluconazole. Refractory infection will require amphotericin B. In addition, it is advisable to avoid ketoconazole in view of drug interactions with other medications employed in the management of AIDS. Herpes eosophagitis responds to acyclovir. Foscarnet is active against acyclovir-resistant herpes simplex. Established infections with CMV usually respond to a course of ganciclovir or forscarnet followed by oral valganciclovir for 21–28 days or until resolution.[31]

Hepatobiliary Disorders

- Most patients will experience hepatobiliary symptoms along the course of their illness. MAI is the most common opportunistic pathogen demonstrated in tissues obtained from liver biopsy, accounting for 38% of the diagnosis in a series. Infection usually occurs late when the CD4 counts are less than 50 cells/mm^3. Hence, the symptomatology is mainly of the systemized illness of disseminated disease although elevation of alkaline phosphatase is typical. The long-term outcome is poor in view of the advanced disease although antimicrobials may produce an initial response. MAI involvement should be distinguished from infections with ***M. tuberculosis***. Extrapulmonary tuberculosis occurs in over 50% of the patients with AIDS. ***M. tuberculosis*** occurs at an early stage of the illness and histology from liver tissue may reveal well-formed caseous granulomatous lesions. Treatment for both typical and atypical tuberculosis should be guided by antimicrobial sensitivities from tissue cultures. Fungi may involve the liver with disseminated disease. Features are mainly with unexplained fever, hepatomegaly and elevated alkaline phosphatase. Fungal abscesses are rarely documented with imaging studies. Hepatic involvement occurs commonly with hematogenous dissemination, as seen with Cryptococcaemia. Less commonly, infections are due to Candida, Coccidioides and Histoplasma. Outcomes of the infection are poor due to disseminated illness and response to extended antifungal therapy is unpredictable. ***Pneumocystis jirovecii (carinii)*** is a fairly common hepatic pathogen in AIDS patients. Involvement occurs in about 38% of the patients. The organism is demonstrable on silver stain, with a characteristic foamy eosinophilic exudate on liver biopsy. Response to parenteral high doses of cotrimoxazole and pentamidine were reported. CMV and Cryptosporidium are associated with acalculous cholecystitis in patients with advanced AIDS. These patients are usually young and present with right upper quadrant pain and abnormal liver profile. Biliary cryptosporidiosis is the most common extraintestinal manifestation of the infection. Clinical features are right upper quadrant pain, nausea, vomiting and fever accompanied by elevated alkaline phosphatase levels. These patients have lower CD4 counts.

Pancreatitis

- The incidence of pancreatitis in patients with AIDS is estimated to be between 4% and 22%. It presents with abdominal pain in patients with advanced HIV disease, occurring because of diverse reasons. Apart from infections, drugs and neoplasia are also responsible for acute pancreatitis in AIDS patients. Possible infectious causes are numerous and include, in decreasing order of occurrence, CMV, ***M. tuberculosis***, ***M. avium***, Cryptococcus, and HSV. Other infectious causes of pancreatitis in AIDS patients are Candida, ***P. carinii, Toxoplama gondii*** and ***Leishmania donovani***. In assessing the patients, there should be a high index of suspicion when given a setting of HIV disease plus abdominal pain and elevated amylase. Fine needle aspiration should be employed for appropriate diagnosis and treatment.

Peritonitis

- Infectious peritonitis in the absence of bowel perforation is being recognized in patients with HIV infection. The clinicians should have a low threshold for consideration of peritonitis even in the absence of liver cirrhosis or peritoneal dialysis, as was found in infection with the ***M. avium*** complex in an AIDS patient. It has also been shown that HIV-infected cirrhotic patients tend to have a higher rate of mortality and higher bacteriological isolates, mainly ***Streptococcus pneumoniae*** infection, than non-HIV cirrhotic patients. Other documented infectious causes are Histoplasma, tuberculosis and Cryptococcus.

Appendicitis

- The condition in AIDS may occur from faecolith, lymphoid hyperplasia or from infections such as acute CMV infection and mycobacterial infection. Clinical presentation is characterized by right lower quadrant pain, which is associated with low to normal white blood cells. However, before surgical treatment a computed tomography scan or laparoscopy should be arranged for because OIs such as typhlitis may mimic appendicitis.

Small And Large Bowel Lesions

- Abdominal pain and diarrhea are common in HIV disease. Diarrhea is, however, the most common GI symptom in HIV/AIDS. Prevalence ranges from 0.9% to 14%. Significantly, prevalence is highest in homosexual men and individuals with lower CD4 counts. Generally, CMV infection is the most common OI of the bowel. A wide variety of protozoal, viral and bacterial pathogens are responsible for diarrhea in AIDS patients. MAI is a unique agent of diarrhea in AIDS patients whereas Cryptosporidium causes self-limiting diarrheal illness in healthy hosts. It is accompanied by chronic diarrhea in immunosuppressed patients. The manifestations of symptoms by enteric pathogen depend on the degree of immunodeficiency judging by the CD4 cell counts. MAI and CMV are seen in the setting of low CD4 counts of $< 100/mm^3$. However, sequel to the availability of HAART and antimicrobial prophylaxis, diarrheal illnesses now also results from both ***Clostridium difficile*** colitis and other side effects of drugs. Sexually transmitted diarrheal pathogens are encountered in patients with multiple sexual partners or receptive anal sex. Initial evaluation should include stool smears and cultures for enteric bacteria. The sample is also sent for ***C. difficile*** toxin in the setting of antibiotic usage. It is encouraged to send at least three stool specimens for ova and parasites and acid fast bacilli smear and tuberculosis cultures. However, it has been shown from previous studies than isolation of pathogens is more likely from watery than from formed stools. Further assessment requires the utilization of sigmoidoscopy to identify, for instance, CMV infection. Colonoscopy is essential for isolated right colonic CMV. Specific therapy is then directed to the enteric pathogen detected. Recurrent infections with Salmonella, Shigella, Campylobacter and Isospora will require administration of alternating antibiotics.

Anorectal Lesions

- The immunosuppressed patient with AIDS is at an increased risk of abscesses, fistulae, fissure and human Papillomavirus infection. The prevalence of anorectal disease among homosexual male patients is high. Fifty-five percent of the 180 consecutive HIV-seropositive patients with anorectal complaints in Chicago were found to be homosexual and bisexual males. Management requires the combination of medical and surgical interventions.

Chronic diarrhea

- Once identifiable infections as well as other causes of diarrhea are investigated and excluded, a unique entity known as AIDS enteropathy can be diagnosed. Known as an idiopathic, pathogen-negative diarrhea, this disease has been investigated extensively. Atypical viral pathogens, including HIV itself, as well as inflammatory and immunologic responses are potential leading causes of it. Although AIDS enteropathy can pose a diagnostic challenge so too does the treatment of it. Highly active antiretroviral therapy, nutritional supplementation, electrolyte replacements, targeted therapy for infection if indicated, and medications for symptom control all are key elements in the treatment regimen. Importantly, a multidisciplinary approach among the gastroenterologist, infectious disease physician, HIV specialists, oncology, and surgery is necessary for many patients.

HIV Enteropathy

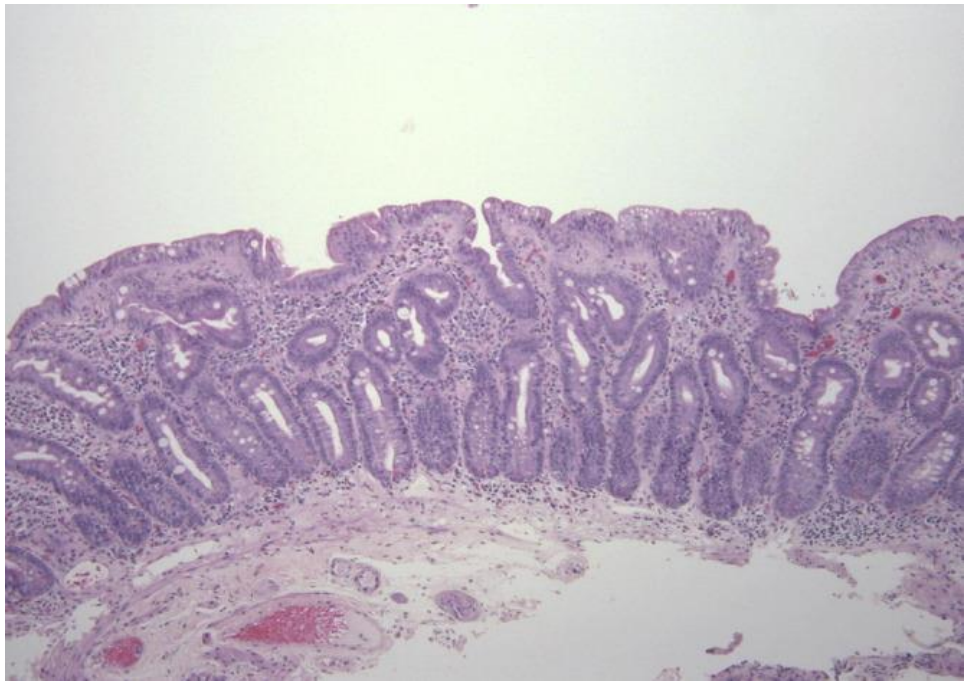
- An interesting entity known as AIDS enteropathy has emerged and evolved over the years and reflects an idiopathic, pathogen-negative diarrhea whose underlying cause might involve undiscovered infectious pathogen(s), inflammatory changes within the GI tract caused by HIV or other environmental/infectious agents, HIV itself, or a complex interplay among any one of these etiologies. AIDS refractory diarrhea can pose diagnostic and treatment challenges. HAART, nutritional supplementation, electrolyte replacements, targeted therapy for specific infections, and alleviation of symptoms are all key elements in the treatment regimen for these patients. The overall care of these challenging patients, from diagnosis to treatment, also involves effective communication and teamwork among a variety of medical and surgical specialties.

HIV Enteropathy

- Over the past 2 decades a well-defined subset of HIV/AIDS patients with profound diarrhea, malnutrition, and wasting, with no infectious pathogen identified as the causative agent, has emerged. In 1987, Kotler et al[3] noted alterations in intestinal plasma cells of AIDS patients without identifiable (at that point in time) intestinal pathogens. In HIV-infected patients with AIDS-related complex or fully expressed AIDS, the mean villus/height and mean villus/crypt ratios were significantly lower than those of normal controls. By using immunofluorescence staining, the researchers observed a decrease in immunoglobulin (Ig)A plasma cells and a relative increase in IgM plasma cells in the small bowel and in the colon. There also was decreased quantitative plasma cell fluorescence in samples that were stained for IgA and IgM, implying less cytoplasmic immunoglobulin per cell.

HIV Enteropathy

Biopsy of small bowel from a patient with AIDS and pathogen-negative diarrhea. Note the prominent villus atrophy, crypt architectural distortion, decrease in crypt/villus ratio, and the significant influx of lymphocytes within the lamina propria.



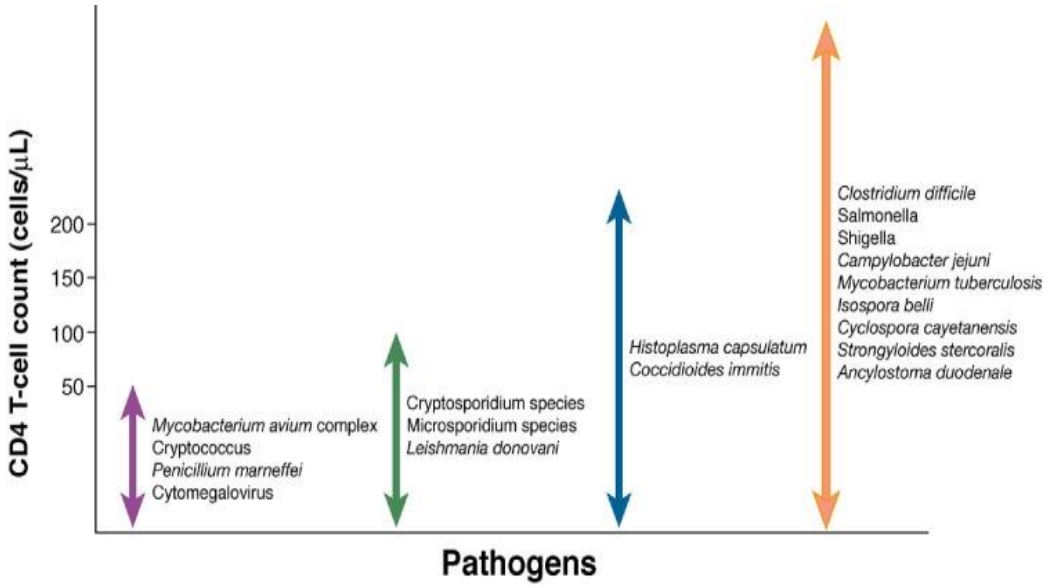
- In 1998, Cunningham et al[4] first identified rotaviruses and adenoviruses by enzyme-linked immunosorbent assay, electron microscopy, and/or cell culture analyses. These 2 viruses were found in more than 50% of HIV-positive symptomatic patients with diarrhea, but in less than 15% of HIV-negative patients, and in less than 20% of HIV-positive asymptomatic patients without diarrhea. It appeared, therefore, that these viruses occasionally were associated with a high excretion rate in HIV-infected patients with diarrhea and might be associated with acute episodes or relapses of diarrhea.

- Grohmann et al,[5] from the Centers for Disease Control, reported in 1993 on the prevalence of a wide range of enteric viruses in HIV-infected patients with and without diarrhea. Sixty-five HIV-positive patients were grouped into those with diarrhea and those without diarrhea. Adenovirus, astrovirus, and picobiranvirus, but not chronovirus, Caliciviridae, or featureless small round viruses were noted in the stools of HIV-positive patients with diarrhea compared with HIV-infected patients without diarrhea. Overall, 35% of the fecal specimens in patients with AIDS and refractory diarrhea harbored 1 or more of these viruses, compared with only 12% of the stools of patients without diarrhea (Table 2). Thus, studies and reports of so-called AIDS enteropathy always should be tempered by the reality that these viruses, as well as other infectious agents, ultimately may be found in patients with so-called idiopathic AIDS-related diarrhea.

Opportunistic infections

- Although HIV enteropathy encompasses an idiopathic, pathogen-negative diarrhea, there is an array of opportunistic infections (OIs) that invade the GI tracts of patients with advanced HIV. GI OIs include a complex milieu of bacteria, fungus, viruses, and protozoa that typically exert their devastating effects when a patient's CD4+ T-cell count decreases to less than 200 cells/µL. The study of GI OIs has undergone an astonishing transformation over the past 25 years, and has been marked by periods of remarkable discovery and innovation in terms of identifying new pathogens and suitable treatments.

Opportunistic infections



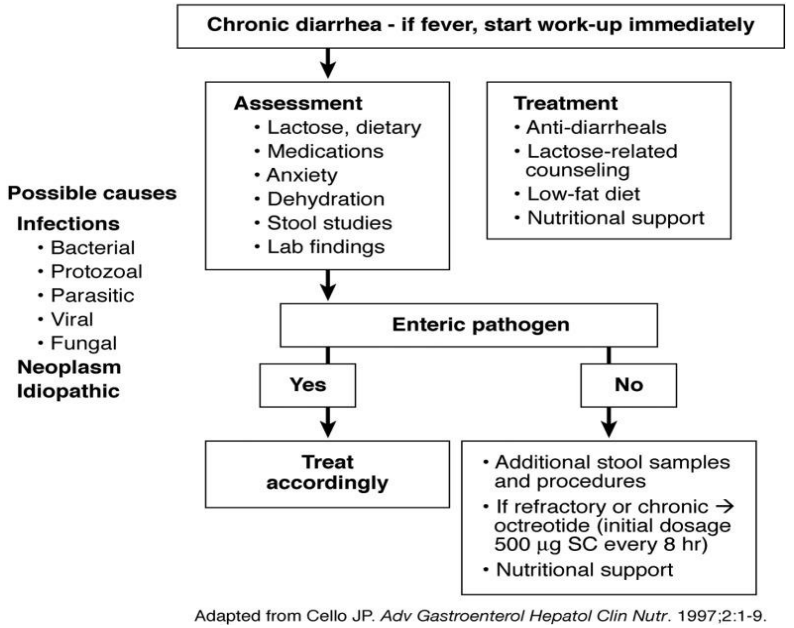
Protozoa		
Cryptosporidia	Combination antiretroviral therapy	•Nitazoxanide 500–1000 mg PO BID for 2 wk •Paromomycin 25–35 mg/kg PO daily for 2 wk •Paromomycin 1 g PO BID + Azithromycin 600 mg PO daily for 4 wk
Cyclospora cayetanensis	Trimethoprim/sulfamethoxazole 160/800 mg PO QID for 1 wk[a]	•Ciprofloxacin 500 mg PO BID for 1 wk •Nitazoxanide 500 mg PO BID for 3 days
Isospora belli	Trimethoprim/sulfamethoxazole 160/800 mg PO QID for 10 days[a]	•Ciprofloxacin 500 mg PO BID for 1 wk •Nitazoxanide 500 mg PO BID for 3 days •Pyrimethamine 50–75 mg PO daily for 3–4 wk

Fungus		
Microsporidia		
Encephalitozoan intestinalis	Combination antiretroviral therapy + Albendazole 400 mg PO BID[b]	
Enterocytozoon bieneusi	Combination antiretroviral therapy	Fumagillin 60 mg PO daily for 2 wk[c]
Histoplasma capsulatum	•Initial phase[d]: liposomal amphotericin B 3 mg/kg IV daily for 2 weeks •Continuation phase[e]: itraconazole 200 mg PO TID for 3 days, then BID for 12 mo	Initial phase[d]: amphotericin B deoxycholate 0.7 mg/kg IV daily for 2 wk
Cryptococcus	•Initial phase: Amphotericin B deoxycholate 0.7 mg/kg IV daily (or liposomal amphotericin B 4–6 mg/kg IV daily) + Flucytosine 25 mg/kg PO QID for 2 wk •Continuation phase: Fluconazole 400 mg PO daily for 8 wk	•Initial phase: Amphotericin B + Fluconazole 400 mg PO/IV daily for 2 wk •Amphotericin B alone •Fluconazole 400–800 mg PO/IV daily + Flucytosine 25 mg/kg PO QID for 4–6 wk •Continuation phase: Itraconazole 200 mg PO BID for 8 wk

Virus		
CMV	•Combination antiretroviral therapy + Ganciclovir 5 mg/kg IV BID for 3–6 wk OR •Foscarnet 90 mg/kg IV BID for 3–6 wk	Valganciclovir 900 mg PO BID for 3–4 wk or until resolution of symptoms[f]

Bacteria		
MAC	Clarithromycin 500 mg PO BID + Ethambutol 15 mg/kg PO daily (±Rifabutin 300 mg PO daily)	See 2008 NIH/CDC/HIVMA/IDSA guidelines for alternative regimens and additional fourth drug options
Mycobacterium tuberculosis	•Initial phase: Isoniazid 5 mg/kg PO daily + Rifampin 10 mg/kg PO daily (or Rifabutin 300 mg PO daily) + Pyrazinamide 15–30 mg/kg PO daily + Ethambutol 15–25 mg/kg PO daily for 2 mo •Continuation phase: Isoniazid 5 mg/kg PO daily + Rifampin 10 mg/kg PO daily (or Rifabutin 300 mg PO daily) for 6 mo	See 2008 NIH/CDC/HIVMA/IDSA guidelines for alternative regimens, treatment for multidrug-resistant TB, patients with liver disease, and/or interactions with HAART
Campylobacter jejuni	Ciprofloxacin 500 mg PO BID for 1–2 wk[g]	Azithromycin 500 mg PO daily for 1–2 wk[g]
Salmonella	Ciprofloxacin 500–750 mg PO BID for 1–6 wk[h]	Trimethoprim/sulfamethoxazole 160/800 mg PO BID for 1–6 wk[h]
Shigella	Ciprofloxacin 500 mg PO BID for 1–2 wk[g]	•Trimethoprim/sulfamethoxazole 160/800 mg PO BID for 1 wk •Azithromycin 500 mg PO on day 1, then 250 mg PO daily for 4 days

Proposed treatment algorithm for patients with AIDS and chronic diarrhea.



Adapted from Cello JP. *Adv Gastroenterol Hepatol Clin Nutr*. 1997;2:1-9.

Pharmacologic agents available for the treatment of noninfectious diarrhea

Antidiarrheal class	Mechanism of action	Examples
Adsorbents	Bulk forming agents that lead to the formation of more viscous stools by absorbing water and binding to other intraluminal contents	Bismuth subsalicylate Kaolin Pectin Psyllium
Antimotility agents	Inhibit peristalsis or propulsive movements in the intestines, thereby reducing fluid and electrolyte loss	Diphenoxylate-atropine Loperamide Octreotide (unlabeled use) Paregoric
Antisecretory agents	Inhibit the secretion of water and electrolytes into the intestines	Bismuth subsalicylate Crofelemer Octreotide (unlabeled use) Zinc Racecadotril (under development)

- A careful analysis of stool samples is an essential and obligatory first diagnostic step. If an enteric pathogen is isolated, the patient should be treated as appropriately as possible with available agents. If after exhaustive stool studies no pathogen is isolated, and no other factors are believed to be contributing to the diarrheal disease, then there is clearly a role for additional, invasive endoscopic evaluations, particularly in those patients who have very severe refractory, dehydrating diarrhea. The decision to perform a complete GI evaluation, consisting of upper endoscopy, small-bowel biopsies, and colonoscopy with biopsies, must be made in conjunction with the patient and their primary care providers. Given the innumerable endoscopic modalities available in gastroenterology and the sophistication of most pathology laboratories, there is little reason to avoid or refuse invasive diagnostic testing in patients who could benefit from targeted therapy.

- Surprisingly, but rarely, patients with profound watery diarrhea and malnutrition will be found to be ingesting agents, either inadvertently or surreptitiously, that are associated with diarrhea. These cathartics include lactose, sorbitol, mannitol, or even over-the-counter cathartics in their diet. These agents clearly should be considered, proscribed, and their intake must be eliminated. Also, it is worthwhile to extensively review a patient's HAART regimen because many HAART medications, and in particular the protease inhibitors such as nelfinavir, fosamprenavir, and ritonavir, are well known to cause diarrhea.

- Antimotility agents (loperamide, diphenoxylate, codeine) and adsorbents (bismuth subsalicylate and kaolin/pectin) are widely available, generally attempted, and somewhat helpful in treating mild to moderate diarrhea.[75] The GI antimotility agents are universally opioids, which decrease stool output by decreasing GI motility and increase transit time, thus generally promoting fluid and electrolyte absorption. These antimotility and adsorbent drugs are all reasonably helpful in patients with mild to moderate pathogen-negative diarrhea. There is insufficient evidence to support the routine use of probiotics and/or herbal remedies in AIDS patients with severe diarrhea. Most patients will have tried several or all of the agents described earlier before seeking medical attention. Additional nonstandard therapies run the gamut of nonsteroidal anti-inflammatory drugs, clonidine, tincture of opium, and octreotide.

Crofelemer **(Mytesi)**

- A predominant type of diarrhea that develops in HIV patients has secretory characteristics, including increased secretion of chloride ions and water into the intestinal lumen. One proposed mechanism that may lead to this type of secretory diarrhea is explained by the activation of the cystic fibrosis transmembrane conductance regulator and calcium-activated chloride channels. Crofelemer is a novel antidiarrheal agent that works by inhibiting both of these channels. The efficacy and safety of crofelemer has been evaluated in clinical trials for various types of secretory diarrhea, including cholera-related and acute infectious diarrhea. More recently, crofelemer was approved by the US Food and Drug Administration for the symptomatic relief of noninfectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy.

Crofelemer **(Mytesi)**

- Results from the ADVENT trial showed that crofelemer reduced symptoms of secretory diarrhea in HIV/AIDS patients. Because crofelemer is not systemically absorbed, this agent is well tolerated by patients, and in clinical trials it has been associated with minimal adverse events. Crofelemer has a unique mechanism of action, which may offer a more reliable treatment option for HIV patients who experience chronic secretory diarrhea from antiretroviral therapy.