Fifth Edition

First Principles of Gastroenterology

The Basis of Disease and an Approach to Management

JANSSEN-ORTHO

A.B.R. Thomson and E.A. Shaffer, editors

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Gastrointestinal Manifestations of Human Immunodeficiency Virus Infection

G.R. May

1. INTRODUCTION

Infection with the human immunodeficiency virus (HIV) and the development of the acquired immunodeficiency syndrome (AIDS) represents a significant problem worldwide. As of the end of 2001 it was estimated that over 40 million persons worldwide were infected with the HIV. In Canada, it is estimated that over 55,000 persons are infected with the HIV, giving an approximate prevalence of 0.3%. The clinical manifestations of HIV infections and AIDS are varied and can involve all organ systems. The gastrointestinal (GI) tract is a common site for opportunistic infections and neoplasms in patients with HIV infection. Over 75% of patients will have significant symptoms related to the gastrointestinal tract at some point during the course of their infection. In many patients GI involvement represents the major manifestation of their HIV infection.

2. BASIC PRINCIPLES OF HIV INFECTION

HIV is a human retrovirus that is acquired predominantly through contact of infected body fluids with the bloodstream, a situation similar to the transmission of hepatitis B virus. It mainly infects the CD4 population of lymphocytes, which perform a helper cell function; immunodeficiency develops as the number of CD4 lymphocytes decreases. Cell-mediated immunity is mainly affected, but there is also impairment in the ability to mount new B-cell–mediated responses. As a result, the patient becomes susceptible to infections and neoplasms. Normal individuals usually have approximately 600–800 x 10^6/mL CD4 lymphocytes. Patients with HIV infection slowly lose their CD4 cells. Opportunistic infections and neoplasms rarely occur until the number of CD4

lymphocytes drops below 300 x 10^6/mL. Certain infections are not seen until CD4 counts are below 100 x 10^6/mL. HIV is also known to infect other cell populations such as macrophages, nerve cells and possibly enterocytes, where it may be clinically latent and act as a reservoir of virus.

Persons recognized to be at high risk for acquiring HIV infection include homosexual or bisexual men, intravenous drug users, hemophiliacs and others who received blood or blood products prior to universal testing of blood in approximately 1985. Heterosexuals who have unprotected intercourse with infected partners are also at risk and at present represent the group with the fastest-rising incidence of HIV infection in North America. In Africa, where HIV infection is endemic, heterosexual transmission through unprotected intercourse is the commonest mode of HIV transmission. When seeing patients with suspected HIV infection, it is important to get an accurate history of risk factors including sexual orientation and practices, history of intravenous drug use, past exposure to blood and blood products and travel to endemic areas.

Many physicians find it difficult to discuss sexual orientation and sexual practices with patients. It is often best to ask the patient directly whether he or she is heterosexual, homosexual or bisexual. For male patients the question can also be addressed by asking the patient if he has ever had sexual relations with other men. Many persons may classify themselves as heterosexual but may have had same-sex sexual experiences. Sexual activity and practices should be ascertained by inquiring about the number of sexual partners in the past and whether the patient has had anal intercourse. Unprotected receptive anal intercourse represents the highest-risk sexual practice for HIV transmission. A history of other sexually transmitted diseases is also important as it suggests high-risk activity, and the presence of open lesions during unprotected intercourse may increase the risk of HIV transmission. It is important to address these issues in a clinical and nonjudgmental way, as negatively phrased questions or judgmental attitudes toward sexual orientation and practices can interfere with the doctor–patient relationship. Patients who perceive a judgmental or negative attitude are less likely to discuss these issues truthfully with the physician.

The acquired immunodeficiency syndrome (AIDS) results from infection with the HIV and the resultant immunodeficiency. The diagnosis of AIDS is usually made on the basis of demonstrating positive serology for HIV with the presence of an opportunistic infection, neoplasm or a CD4 lymphocyte count less than 200 x 10^6/mL. At present it appears that most patients with untreated HIV infection will eventually progress to AIDS; however, the rate of progression is variable. It has been well documented that therapy with antiretroviral drugs slows the progression of HIV infection to AIDS and prolongs

the life of patients with established AIDS. Several classes of antiretroviral drugs are now available to treat the HIV, including nucleoside reverse transcriptase inhibitors (e.g., AZT, 3TC), protease inhibitors (e.g., saquinavir, ritonavir and indinavir) and non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, nevirapine). It is well established that using highly active antiretroviral therapy (HAART) which consists of combination therapy with three or more drugs is more effective than using one or two drugs and reduces the incidence of drug resistance. Combination therapy with these agents has had dramatic clinical effects with most patients showing improvements in CD4 counts and suppression of HIV replication. Current recommendations for initiation of antiretroviral therapy are based upon the CD4 lymphocyte count and HIV viral load. In general antiretroviral therapy should be started once the CD4 lymphocyte count falls below 350 x 10^6/mL. Therapy may be started in some individuals with CD4 counts greater than 350 x 10^6/mL if the viral load is also high. With advancing immunosuppression, the common occurrence of certain opportunistic infections such as Pneumocystis carinii pneumonia, Mycobacterium avium-intracellulare and toxoplasmosis has also prompted recommendations for prophylactic therapy.

3. GASTROINTESTINAL INVOLVEMENT IN HIV INFECTION

3.1 General Considerations

The GI tract represents a common site of involvement of opportunistic infection and neoplasms in HIV infection. GI symptoms such as dysphagia, abdominal pain, diarrhea and weight loss are common and affect over 75% of patients with HIV infection at some time during the course of their disease. It is important to remember that HIV-infected patients may also have common gastrointestinal problems unrelated to the HIV infection. The approach to HIV-infected patients with gastrointestinal symptoms should be guided by the CD4 count. In patients with counts greater than 300 x 10^6/mL an opportunistic infection or neoplasm is very unlikely, and the approach to investigation of these patients should be similar to that in immunocompetent individuals. Once the CD4 count falls below 300 x 10^6/mL the risk for opportunistic problems increases, and they must be considered in the differential diagnosis.

Other issues that must be considered in the evaluation of HIV-positive patients with gastrointestinal symptoms are drug side effects and problems specific to risk factor groups. Many of the antiretroviral drugs and antimicrobials used in HIV infection have prominent GI side effects, which are often overlooked in the differential diagnosis of GI problems in these patients. Homosexual males are also at risk for a variety of gastrointestinal problems as a result of their sexual practices. This includes an increased risk

of gastrointestinal parasitic infections and proctitis resulting from gonorrhea, syphilis or Chlamydia. Patients practicing receptive anal intercourse are at risk for rectal trauma manifesting as lacerations, fissures and perianal infections. Intravenous drug users are also at risk for infection with hepatitis B and hepatitis C viruses.

3.2 Bacterial Infections

Typical enteric bacterial pathogens such as nontyphoidal strains of Salmonella, Shigella species and Campylobacter jejuni occur with only a slightly increased frequency in HIV-infected patients. When they do occur in immunocompromised patients the presentation is often atypical with a high incidence of bacteremia in addition to the typical symptoms of enteritis or colitis. Immunocompromised HIV patients also appear to be unable to effectively eradicate these organisms so that recurrent infection is common, often necessitating the use of chronic antibiotic suppression. Diagnosis is made with stool cultures. Because of the high incidence of bacteremia, blood cultures should also be done in patients presenting with acute diarrhea and fever.

The principles of treatment for acute bacterial enteritis or colitis in HIV-infected patients are generally the same as for other patients, with supportive care and intravenous fluids as required. Immunocompetent patients will usually clear the infection, and indications for antibiotic therapy are the same as for other patients. Immunocompromised patients and those with bacteremia should be treated with appropriate antibiotics (Table 1). Chronic suppressive therapy is often required as a result of the high incidence of recurrent infection.

3.3 Mycobacterial Infections

3.3.1 MYCOBACTERIUM AVIUM-INTRACELLULARE

Mycobacterium avium-intracellulare (MAI) is an atypical mycobacterium of environmental origin that is a common opportunistic infection in immunocompromised HIV-infected patients (CD4 lymphocyte counts < 100 x 10^6/mL) and is an AIDS-defining illness. It usually presents as a chronic systemic illness including fever, night sweats, weight loss and lymphadenopathy in addition to diarrhea. The diarrhea is often mild to moderate in severity and may have features to suggest malabsorption. Hepatosplenomegaly is a common finding on examination, as the liver and spleen are also commonly involved in MAI infection. The organism commonly infects the small bowel mucosa where it causes thickening and blunting of the villi as a result of an increased number of macrophages in the lamina propria. The appearance on hematoxylin and eosin stains is strikingly similar to Whipple's disease. With mycobacterial stains the macrophages can be seen to be filled with acid-fast

TABLE 1. Treatment regimens for HIV-related gastrointestinal infections

Organism	*Drug of first choice*	*Alternative treatments*
Bacteria		
Salmonella	Ceftriaxone 1–2 g IV q12–24h	Ciprofloxacin 500 mg q12h Trimethoprim-sulfamethoxazole 160 mg/800 mg po bid
Shigella	Ciprofloxacin 500 mg po bid	Trimethoprim-sulfamethoxazole 160 mg/800 mg po bid Ceftriaxone 1–2 g IV q12–24h
Campylobacter	Ciprofloxacin 500 mg po bid or Erythromycin 500 mg po qid	Tetracycline 500 mg po qid
Mycobacteria		
Mycobacterium tuberculosis	Isoniazid 300 mg po qd + Rifampin 600 mg po qd + Pyrazinamide 15–25 mg/kg po qd + Ethambutol 15–25 mg/kg po qd or Streptomycin 15 mg/kg IM qd	Depends upon sensitivity patterns
Mycobacterium avium-intracellulare	Clarithromycin 500–1,000 mg po bid + one or more of: Ethambutol 15–25 mg/kg po qd Clofazimine 100–200 mg po qd Ciprofloxacin 750 mg po bid Amikacin 7.5–15 mg/kg IM qd	Rifabutin 450–600 mg po qd + one or more of the other agents
Fungi		
Candida albicans (oral)	Clotrimazole troches 100 mg po 1–3 times/day Fluconazole 100 mg po qd	Ketoconazole 200 mg po qd Itraconazole 200 mg po qd
(esophageal)	Fluconazole 100–200 mg po qd	Ketoconazole or itraconazole 200 mg po qd Amphotericin B 0.3 mg/kg IV qd x 7 days
Histoplasmosis	*Initial therapy:* Amphotericin B 0.5–0.6 mg/kg IV qd for 4–8 weeks *Chronic suppression:* Itraconazole 200 mg po bid	Itraconazole 200 mg po bid Amphotericin B 0.5–0.8 mg/kg IV weekly

(cont'd)

TABLE 1. Treatment regimens for HIV-related gastrointestinal infections (cont'd)

Organism	*Drug of first choice*	*Alternative treatments*
Parasites		
Giardia lamblia	Metronidazole 250 mg po tid	Quinacrine hydrochloride 100 mg po tid
Entamoeba histolytica	Metronidazole 750 mg po tid x 10 d followed by Iodoquinol 650 mg po tid x 20 d	
Cryptosporidium	Supportive fluid therapy Loperamide 2–24 mg po qd	Paromomycin 500–750 mg po qid Octreotide 50–500 µg sq tid
Microsporidium	Supportive fluid therapy Loperamide 2–24mg po qd	Albendazole 400 mg po bid Octreotide 50–500 µg sq tid
Isospora belli	Trimethoprim-sulfamethoxazole 160 mg/800 mg po qid x 10 d then bid x 21 d	Pyrimethamine 50–75 mg qd x 21 d
Viruses		
Herpes simplex virus	*For active lesions:* Acyclovir 200 mg po 5 times/day Famciclovir 500 mg po tid Valacyclovir 1,000 mg po tid *For maintenance therapy:* Acyclovir 400 mg po bid	Foscarnet 40 mg/kg IV q8h x 21 d Foscarnet 40 mg/kg IV qd
Cytomegalovirus	*For active disease:* Ganciclovir 5 mg/kg IV q12h x 14–21 d *For maintenance therapy:* Ganciclovir 5 mg/kg IV qd or 6 mg/kg IV qd 5 times/week	Foscarnet 60 mg/kg IV q8h x 14–21 d Foscarnet 90–120 mg/kg IV qd

organisms. In addition to the liver and spleen, the intra-abdominal lymph nodes and bone marrow are also commonly involved with MAI. Diagnosis can usually be made with blood and stool cultures. Blood cultures will usually be positive within 3–4 weeks, as this is a rapidly growing mycobacterium. Barium radiographs of the small bowel will often show dilation of the small bowel and irregular thickening of the small bowel folds. Ultrasound or CT scan of the abdomen will document hepatosplenomegaly, and there will often

be enlarged intra-abdominal lymph nodes. Small bowel biopsy showing typical histology can also be used to establish a diagnosis.

Therapy for MAI is difficult and requires combinations of 4–6 antituberculous drugs, and the results are generally poor (Table 1). The organism usually cannot be eradicated; the goal of therapy is chronic suppression. Drug side effects are common, and many patients are unable to tolerate full therapy. Despite treatment, many patients have progressive symptoms and wasting. Because of the difficulty in treating established MAI infection, prophylactic therapy is recommended, and recent studies have shown some benefit to using either rifabutin 300 mg p.o. daily or azithromycin 1,250 mg p.o. weekly, once the patient's CD4 cell count falls below 100 x 10^6/mL.

3.3.2 MYCOBACTERIUM TUBERCULOSIS

Pulmonary Mycobacterium tuberculosis (TB) is being seen with increased frequency in HIV-infected patients and is especially common in IV drug users. In HIV infection the GI tract may be involved with extrapulmonary TB either as direct extension from pulmonary lesions, where the esophagus is usually involved, or from systemic spread, where any part of the GI tract including liver and pancreas may be involved. Isolated involvement of the GI tract is unusual. Diagnosis should be made with biopsy and culture of the most readily accessible lesions. It is important to culture and do drug sensitivities on isolates of TB because of the rising incidence of multiple drug resistance in this patient population. Initial therapy should include three or four antituberculous drugs. Choice of drugs should be determined on the basis of local sensitivity patterns.

3.4 Fungal Infections

3.4.1 CANDIDA ALBICANS

Candida albicans is one of the most common opportunistic infections in HIV-infected patients. Oropharyngeal candidiasis occurs frequently and is often one of the earliest clinical signs of immune impairment. When limited to the oropharynx it is often asymptomatic or associated with mild discomfort. Esophageal involvement is usually associated with dysphagia; however, many patients may have only vague epigastric discomfort during meals. Odynophagia can occur with esophageal candidiasis, but severe pain with swallowing is unusual and suggests other infections such as cytomegalovirus (CMV), herpes simplex virus (HSV) or nonspecific HIV-associated esophageal ulceration. Patients with esophageal involvement usually have evidence for oropharyngeal Candida, commonly seen as whitish plaques on the buccal mucosa and posterior oropharynx.

Esophageal involvement may occasionally occur in the absence of oral Candida, but this is unusual.

Candidal esophagitis can be demonstrated with a barium swallow that shows abnormalities ranging from small filling defects on the mucosal surface representing mucosal plaques to thickening of the mucosal folds with a shaggy outline to the wall. Severe or deep ulcerations may be seen but are unusual. Diagnosis is best made with endoscopy, which shows typical white adherent pseudomembranous plaques. In severe cases the entire esophageal mucosa may be covered with a confluent white membrane. The diagnosis is confirmed by brush cytology or mucosal biopsy showing invasion of the candidal pseudohyphae into the squamous epithelium. Cultures are not routinely done, as these organisms are commonly present in normal individuals and tissue invasion should be demonstrated to confirm the diagnosis.

Oropharyngeal candidiasis can be treated with either local therapy using clotrimazole troches 100 mg p.o. 1–3 times/day or with systemic antifungals such as fluconazole 100 mg p.o. daily. Esophageal involvement should be treated with one of the oral antifungal agents, as topical agents are generally not effective. Higher doses may be required for initial treatment in symptomatic patients (Table 1). Initial therapy should continue for approximately 14 days. Recurrence is common, and many patients require ongoing therapy with an oral antifungal agent. Resistance to oral antifungal agents is starting to emerge. Intravenous amphotericin B can be used in low doses for those who fail therapy with oral antifungal agents. Esophageal candidiasis is so common in HIV infection that many experts recommend empiric therapy in patients with esophageal symptoms, especially if oral Candida is present. Further investigation with endoscopy can be reserved for those who do not respond to empiric antifungal therapy or for those with atypical symptoms. Disseminated infection with Candida may occur in HIV infection but is unusual, as the infection usually remains mucocutaneous. Disseminated infection has a poor prognosis and is often fatal.

3.4.2 OTHER FUNGAL INFECTIONS

Other fungal infections seen in HIV infection include cryptococcosis, histoplasmosis and coccidioidosis. Disseminated infection of any of these fungi establishes a diagnosis of AIDS when present with a positive HIV antibody test. The incidence of these infections varies, and they are usually seen in patients who have lived in or have visited endemic areas. Clinically, patients usually present with prominent systemic symptoms such as fevers, night sweats and weight loss. Neurologic involvement is usually seen with cryptococcosis. With histoplasmosis, the liver is often involved as part of a disseminated infection producing abnormalities of liver chemistry. Diagnosis of

these infections generally depends on the demonstration of fungi through examination or culture of clinical specimens. Serologic tests are not dependable in the immunocompromised patient. Therapy usually requires intravenous amphotericin B in high doses. The response to therapy is generally poor, with a high rate of relapse and a poor overall prognosis.

3.5 Intestinal Parasitic Infections

3.5.1 GIARDIASIS

Giardia lamblia is a common intestinal parasitic infection that is commonly seen in homosexual or bisexual males. Its increased frequency in HIV patients is likely due to the high frequency in homosexual men rather than as a direct result of the HIV infection, as it does not appear to have a significantly higher incidence in other risk groups. Transmission occurs via the fecal–oral route. It usually infects the small bowel mucosa where it may be asymptomatic but usually causes diarrhea with abdominal cramping, bloating and nausea. In severe cases it may produce malabsorption and steatorrhea. Dissemination is rare and does not appear to be a significant problem in HIV infection.

The diagnosis depends upon demonstrating Giardia in the stool with an examination for ova and parasites. It may also be diagnosed on a duodenal aspirate or duodenal biopsy taken at the time of endoscopy. Treatment with metronidazole 250 mg p.o. t.i.d. for 5 days is usually effective in eradicating the organism even in HIV-infected patients; alternatively, quinacrine 100 mg p.o. t.i.d. for 5 days can be used.

3.5.2 ENTAMOEBA HISTOLYTICA

Entamoeba histolytica is an intestinal ameba that is also seen with increased frequency in HIV-infected patients as a result of its increased frequency in homosexual and bisexual males. It usually causes colitis with bloody diarrhea and abdominal cramps. Asymptomatic carriage is seen more commonly in HIV-infected patients than in patients with amebiasis who are not infected with the HIV. Dissemination is rare and is not seen more frequently in HIV-infected patients than in other patients with Entamoeba histolytica infection. Diagnosis is made by demonstrating ameba on a stool examination for ova and parasites. Sigmoidoscopy may show evidence for colitis, and typically Entamoeba histolytica infection causes punched-out “flask-shaped” ulcers. Diagnosis can be confirmed by demonstrating organisms on biopsy or from a fresh stool aspirate.

Therapy for symptomatic Entamoeba histolytica infection is with metronidazole 750 mg p.o. t.i.d. for 10 days followed by iodoquinol 650 mg p.o. t.i.d. for 20 days. Asymptomatic carriers may just be treated

with iodoquinol. Patients should have follow-up stool studies to confirm the eradication of the infection.

3.5.3 CRYPTOSPORIDIUM

Cryptosporidium is a protozoal parasite that is now recognized as a cause of self-limited diarrhea in immunocompetent persons. Several epidemic outbreaks have been identified. In immunocompromised patients it causes chronic watery nonbloody diarrhea that can be severe, leading to significant dehydration with electrolyte disturbances and death. Patients may have associated abdominal cramps and bloating, but these are not usually severe. Crypto-sporidiosis is an AIDS-defining illness in HIV-infected patients.

The diagnosis of Cryptosporidium infection is based upon the demonstration of cryptosporidial oocysts in stool or on mucosal biopsy from the small intestine or colon. Involvement of the bowel may be patchy and involve the ileum, so intestinal biopsy from the duodenum or distal colon is not reliable and examination of the stool is the best diagnostic test. Recently, special stains have been developed, which have increased the yield of diagnosis from stool tests. Therapy in immunocompromised patients usually is supportive with the use of intravenous fluids as necessary to correct volume depletion and antidiarrheal agents such as loperamide 2–24 mg per day to keep diarrhea under control. In severe cases where diarrhea cannot be controlled with antidiarrheal agents, the somatostatin analogue octreotide has been used successfully in doses ranging from 50 μg to 500 μg s.q. t.i.d. to control the diarrhea. To date, there is no proven therapy to specifically treat and eradicate Cryptosporidium. Trials using spiramycin and paromomycin have been reported, but the results have been disappointing.

3.5.4 MICROSPORIDIUM

Microsporidia are a group of intracellular protozoans that measure 1–2 μm in size and have been described in HIV-infected patients. The commonest organisms of this group identified are Enterocytozoon bieneusi and Septata intestinalis. They are believed to be pathogenic in most patients, but asymptomatic carriage in HIV patients has been documented. When symptomatic, infection with Microsporidium resembles that of Cryptosporidium, usually with watery nonbloody diarrhea of variable severity, mild abdominal cramps and bloating.

When these organisms were initially described, the diagnosis required electron microscopy of a small bowel biopsy to see the small intracellular parasites. More recently, special stains have been developed to detect Microsporidia in stool samples. Experienced pathologists can usually see the organisms with high-power microscopy of thin plastic sections of mucosal biopsies. Therapy of symptomatic microsporidial infection is similar to that of

Cryptosporidium, with the use of supportive therapy and antidiarrheal agents. Octreotide has also been used successfully for severe watery diarrhea. Metronidazole and albendazole have been used to try to eradicate Microsporidium, but neither has been shown to be reliably effective.

3.5.5 ISOSPORA BELLI

Isospora belli is another intestinal protozoal parasite that has been identified as causing infection in the setting of HIV, and infection with Isospora belli is also an AIDS-defining illness. Uncommon in North America, it has been seen in up to 15% of Haitian patients with AIDS. Clinically it causes a nonspecific nonbloody watery diarrhea similar to that of Cryptosporidium. Diagnosis is usually easily made by examination of stool for ova and parasites. Unlike infection with Cryptosporidium and Microsporidium, isoporiasis can usually be treated successfully with trimethoprim-sulfamethoxazole 160 mg tmp/800 mg smx p.o. q.i.d. for 10 days, then b.i.d. for 3 weeks. Recurrence is common (approximately 50%), and some patients may need chronic therapy.

3.5.6 STRONGYLOIDES STERCORALIS

Strongyloides stercoralis is a nematode endemic in tropical areas. It usually infects a host by penetrating the skin as filariform larvae. The larvae then travel via the bloodstream to the lungs where they leave the alveolar capillaries, are coughed up and swallowed. Once they reach the small intestine they release eggs that develop into infective filariform larvae that burrow into the small bowel mucosa. Pruritus, papillary rashes and edema may occur at the site of skin entry. Intestinal involvement may result in fever, nausea, vomiting, diarrhea, abdominal pain and weight loss. Diagnosis can best be made by examination of duodenal aspirate but can also be done by examination of concentrated stool specimens. Treatment is usually successful with thiabendazole 50 mg/kg/day in 2 doses for 2 days. Disseminated strongyloidiasis may occur in immunocompromised individuals and is recognized as an AIDS-defining illness. Therapy in immunocompromised individuals may need to be continued for at least 7 days, and some may require chronic therapy.

3.5.7 PNEUMOCYSTIS CARINII

Pneumocystis carinii is recognized as a common cause of pulmonary infection. Extrapulmonary infections of Pneumocystis have been recognized especially in patients who have received aerosolized pentamidine rather than systemic therapy for Pneumocystis carinii pneumonia (PCP) prophylaxis. Infection of the liver, spleen, intestine, bone marrow and peritoneal cavity (producing ascites) have all been reported. Diagnosis is made by demonstrating typical organisms on a

methenamine-silver stain of clinical specimens. Therapy is similar to that of pneumocystis pneumonia.

3.6 Viral Infections

3.6.1 CYTOMEGALOVIRUS

Cytomegalovirus is a common infection, with greater than 50% of Canadian adults showing serologic evidence of previous exposure to CMV. Homosexual men and intravenous drug users have a seroprevalence of CMV as high as 90%. In immunocompetent patients the infection is latent and rarely causes clinical illness. Reactivation of latent infection occurs as HIV-infected patients become immunocompromised and is usually seen when the CD4 lymphocyte count is below 50 x 10^6/mL. CMV infection is increasing as an important clinical problem in HIV patients.

The two most common sites for CMV infection in HIV-infected patients are the retina and gastrointestinal tract. The infection can involve any part of the GI tract, where it produces ulcerating lesions. The esophagus and colon are the most common sites of GI involvement. Esophageal involvement usually presents with odynophagia and dysphagia. Endoscopy shows large shallow ulcerations that may be circumferential. Involvement of the colon produces an acute colitis presenting with diarrhea that may be bloody, often with severe abdominal pain. Sigmoidoscopy or colonoscopy shows a colitis with friable edematous mucosa and scattered ulcerations, a picture similar to Crohn's disease. Small intestinal, gastric and hepatic involvement are less common. Since CMV is commonly found in HIV patients, culture of virus from mucosal biopsies is not sufficient to make a diagnosis of CMV infection. The diagnosis is based upon demonstrating the presence of intranuclear inclusion bodies in biopsy specimens. The presence of an accompanying vasculitis with viral inclusions in endothelial cells further supports CMV as the cause of the lesion. Systemic infection can be confirmed by viral cultures of white blood cells from the buffy coat of a centrifuged specimen of blood.

Therapy of symptomatic CMV requires ganciclovir 5 mg/kg IV q12h initially for 14–21 days. Foscarnet 60 mg/kg IV q8h for 14–21 days can be used as an alternative. These treatments usually result in clinical improvement and healing of mucosal lesions. Recurrence is high, however, and many experts recommend chronic suppressive therapy with ganciclovir 6 mg/kg IV daily 5 times per week or foscarnet 90–120 mg IV daily after acute therapy. Chronic therapy appears to be required as long as the patient remains immunocompromised with CD4 lymphocyte counts less than 200 x 10^6/mL. In patients who respond to antiretroviral therapy so that their CD4 lymphocyte counts improve to greater than 200 x 10^6/mL, chronic maintenance therapy for

cytomegalovirus (CMV) can be discontinued. Oral formulations of ganciclovir which have been shown to be effective for chronic suppression of CMV retinitis have not been shown to be effective for gastrointestinal involvement with CMV.

3.6.2 HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV) most commonly infects the esophagus to produce multiple esophageal ulcerations. Clinically herpetic esophagitis presents with prominent odynophagia and dysphagia that are indistinguishable from symptoms of CMV esophagitis. Differentiation from other causes of esophagitis in these patients requires endoscopy. The ulcers produced by herpes simplex virus are usually multiple and small. Biopsies will show multi-nucleated giant cells and Cowdry type A intranuclear inclusion bodies. Viral culture of biopsy material should be positive for HSV.

HSV esophagitis can usually be treated effectively with oral acyclovir 200 mg p.o. 5 times per day, famciclovir 500 mg p.o. t.i.d. or valacyclovir 1,000 mg p.o. t.i.d. In patients unable to take oral medications due to odynophagia, acyclovir can be given intravenously in a dose of 5 mg/kg q8h. Initial therapy should continue for 10–14 days. Recurrence is common, and many patients require chronic therapy with one of the oral agents. Foscarnet has been used as alternative therapy in those who have failed therapy with the other antiviral agents.

3.6.3 HUMAN IMMUNODEFICIENCY VIRUS

It is not clear whether the HIV itself causes gastrointestinal pathology. Two situations where direct pathologic effect of the HIV in the GI tract is suspected are nonspecific esophageal ulcerations and HIV enteropathy. Esophageal ulcerations are most commonly due to CMV and herpes virus, as discussed above. Ulcerations thought possibly to be directly due to the HIV occur as one of the seroconversion syndromes and as the idiopathic nonspecific esophageal ulcers seen in later stages of HIV infection. Acute infection with the HIV is usually associated with a nonspecific viral illness. As part of this seroconversion syndrome some patients develop severe odynophagia and are found on endoscopy to have multiple superficial esophageal ulcers. Electron microscopy of these ulcers has shown viral particles consistent with retroviruses. The ulcerations and odynophagia typically spontaneously resolve.

Later in the course of HIV infection, esophageal ulcerations may occur which are negative for the usual pathogens. These ulcers are usually deep with undermined edges and may be multiple. Although usually found in the esophagus, they can also occur in the posterior pharynx. Symptomatically they present with severe odynophagia that often limits oral intake. Interestingly

they usually respond dramatically to treatment with corticosteroids taken orally or injected intralesionally. The etiology of these lesions is not clear; the dramatic response to steroids and other immune modifiers such as thalidomide implies an immunologic basis to the ulcerations.

HIV enteropathy is a term that has been applied to describe chronic diarrhea, often accompanied by weight loss, where no identifiable pathogen can be found. It is unclear if this enteropathy is due to an unidentified pathogen or to a direct effect of the HIV on the gut. The HIV potentially could affect the gut directly by infecting enterocytes, or indirectly by inducing the local release of cytokines and other inflammatory mediators, which then may affect enterocyte function. Treatment should concentrate on controlling the underlying HIV infection with HAART and symptomatic treatment of the diarrhea.

3.7 Neoplasms

3.7.1 KAPOSI'S SARCOMA

Kaposi's sarcoma (KS) is the most common neoplasm seen in HIV-infected patients. It has been more common in homosexual or bisexual males than in other risk groups for HIV infection, and its incidence appears to be decreasing within this risk group. An infective cofactor has been postulated to explain the epidemiology of HIV-related KS, although such a factor has not been definitely identified. KS predominantly involves the skin and oropharynx; gastrointestinal involvement is seen in up to 40% of patients with skin involvement. Rare cases of visceral KS in the absence of skin lesions have been reported.

In most cases, GI involvement with KS is asymptomatic. Mucosal lesions can occur throughout the GI tract and are usually incidentally found at endoscopy, where they appear as raised red to violaceous macules. Large lesions may be nodular and may ulcerate. Symptoms are usually the result of hemorrhage from ulceration or obstruction from bulky lesions. Diarrhea and protein-losing enteropathy have also been reported. The exact presentation will depend upon the location of the lesions in the GI tract. Visceral KS should be suspected in any HIV patient with skin KS who has GI symptoms.

The diagnosis is made by histologic examination of mucosal biopsies. A recently described infection, bacillary angiomatosis, has similar histology to KS; differentiation is made by demonstrating organisms on silver stains. Gastrointestinal involvement with bacillary angiomatosis has also recently been described. HIV-related KS can be treated by local or systemic therapy. Oral lesions are best treated with local radiation or laser excision. Symptomatic visceral involvement requires systemic therapy, usually with combination chemotherapy. Good responses to subcutaneous or intralesional interferon have also recently been reported.

3.7.2 LYMPHOMA

B-cell lymphomas represent the second most common neoplasm occurring in HIV-infected patients. These are usually high-grade lymphomas of the large cell type; however, patients with Burkitt's lymphoma and Hodgkin's disease have also been reported. The gastrointestinal tract represents the second commonest site of involvement after the central nervous system. The lymphomas occurring in HIV infection are commonly extranodal.

Any part of the gastrointestinal tract can be involved, with the presentation and symptoms depending on the particular site. Systemic symptoms of fevers, night sweats and weight loss are commonly associated. The diagnosis is made by histologic examination of material obtained from endoscopy, or ultrasound- or CT-guided biopsy. Treatment requires combination chemotherapy similar to that for other high-grade lymphomas. Tolerance of therapy is generally poor, often as a result of the poor functional status of these patients when they develop lymphoma and the presence of other opportunistic infections. Full remissions can occur in patients who can tolerate combination chemotherapy, but the prognosis is generally poor.

3.7.3 ANAL CARCINOMA

Squamous cell carcinoma of the anal canal is seen with higher frequency in homosexual and bisexual men who practice anoreceptive intercourse. The increased risk is independent of HIV infection and, like cervical carcinoma in women, appears to be related to previous infection with human papilloma virus. Colorectal carcinoma is not seen with higher frequency in this risk group. Anal carcinoma may present with a mass and associated fissure or fistula. Local pain is usually present and there may be bleeding. The differential diagnosis includes infections such as syphilis, lymphogranuloma venereum and condyloma acuminatum, and benign perianal conditions of fissure in ano and anal trauma from intercourse or instrumentation. Definitive diagnosis is made through biopsy of suspicious lesions, especially those that fail to heal after treatment of any secondary infections. Treatment modalities include surgical excision, but many may be treated with combined radiation and chemotherapy, which has effected cures with good preservation of anorectal function.

4. HEPATOBILIARY AND PANCREATIC INVOLVEMENT IN HIV INFECTION

The liver is commonly involved during the course of HIV infection, with hepatomegaly and/or abnormal liver chemistry being seen in approximately 60% of AIDS patients. Involvement of the biliary tree and gallbladder is much less common. Hepatic disease may occur as a result of opportunistic infections (HSV,

CMV, MAI, fungi) or neoplasms (KS, lymphoma). In such cases the liver is usually involved as part of more diffuse systemic involvement and is rarely the sole site of infection. Other infections such as hepatitis B and hepatitis C are common as a result of associated risk factors such as intravenous drug use and sexual transmission. Malnutrition, alcohol and hepatotoxicity of medications are other common factors that should be considered in the evaluation of hepatic abnormalities in these patients.

Co-infection of HIV with either hepatitis B or hepatitis C virus is often seen as a result of common risk factors. The effect of HIV-related immunosuppression on chronic hepatitis B often results in clinical improvement of the chronic hepatitis. Since it is the immune reaction to hepatitis B that causes the hepatic inflammation, biochemical parameters of hepatitis often improve, as does the activity on liver biospy as the HIV-associated immunosuppression progresses. Despite the clinical improvement, hepatitis B viral replication increases. Hepatitis C, on the other hand, is directly hepatotoxic, and advancing immunosuppression is not uncommonly associated with worsening of the hepatitis and progressive liver disease.

Complications resulting from liver disease caused by hepatitis B or C previously were not commonly seen, since patients would often not survive long enough for end-stage liver disease to develop. As a result of this, specific treatment of hepatitis B or C was generally not recommended and was associated with a poor response. With the advent of HAART, patients with HIV infection are surviving longer and those patients that have co-infection with either hepatitis B or C are at risk for developing complications of chronic liver disease. Specific therapy for the viral hepatitis should be considered in these co-infected patients. Patients with hepatitis B and evidence of active liver disease should receive lamivudine (3TC) as part of their antiretroviral regimen as it has potent activity against the hepatitis B virus in addition to its antiretroviral activity. Patients co-infected with HIV and hepatitis C who have evidence of active hepatitis should be considered for specific hepatitis C therapy. Studies have shown that in patients with well controlled HIV infection the results of combination therapy with standard or pegylated interferon and ribavirin for hepatitis C are equivalent to those seen in HIV negative patients. Drug related side effects such as thrombocytopenia and neutropenia may be more prevalent in HIV patients and close monitoring is required.

Biliary involvement in HIV infection is commonly termed *AIDS cholangiopathy* and results from inflammation of the biliary tree and gallbladder. There can be a spectrum of involvement ranging from acute acalculous cholecystitis to papillary stenosis with bile duct obstruction or more diffuse involvement of the biliary tree producing a picture similar to sclerosing cholangitis. Cholangiopathy is most commonly due to CMV infection of the biliary tree but

has also been reported to result from biliary infection with Cryptosporidium or Microsporidium. Acute acalculous cholecystitis presents with RUQ pain, fever and tenderness on examination. Cholecystectomy is usually required. Cholangiopathy may present with less acute RUQ pain, fever and nausea, with cholestatic liver enzyme abnormalities. Diagnosis of cholangiopathy is made by ERCP. Patients with dilated common bile ducts who presumably have papillary stenosis secondary to an acute papillitis have responded symptomatically to endoscopic sphincterotomy. Patients in whom CMV is proven or suspected as the cause may improve with specific treatment for CMV. Rarely Kaposi's sarcoma or lymphoma can involve the gallbladder or biliary tree.

Symptomatic pancreatic involvement in HIV infection is not common, but clinically will usually present as acute pancreatitis. Asymptomatic elevations of serum amylase or lipase are common and are seen in up to 45% of patients. These are often related to medications but may also be due to asymptomatic involvement of the pancreas with opportunistic infection or neoplasm. Acute pancreatitis presents in a similar manner in patients with and without HIV infection. In addition to the commonly recognized causes of pancreatitis, other possibilities need to be considered in HIV patients. Drugs commonly used in HIV patients, including sulfonamides, pentamidine and the reverse transcriptase inhibitor dideoxyinosine (ddI), are common causes of pancreatitis. Pancreatic involvement with opportunistic infection and neoplasm, although usually asymptomatic, may cause pancreatitis. The principles of treatment of acute pancreatitis are the same for HIV-infected patients as for those without HIV infection. Drugs potentially involved should be stopped. Where no obvious etiology is apparent, CT scan of the pancreas is useful to rule out focal lesions that might indicate infections or neoplasms involving the pancreas.

5. NUTRITIONAL CONSIDERATIONS AND THE WASTING SYNDROME

Weight loss is a common problem in HIV infection, especially in the more advanced stages of AIDS. Weight loss of greater than 40% of lean body mass is an independent predictor of mortality. Weight loss of greater than 10% of body weight with no obvious underlying opportunistic infection or neoplasm has been termed *the HIV wasting syndrome* and is an AIDS-defining illness. The cause of weight loss in HIV-infected patients is multifactorial and includes diminished intake, malabsorption and increased metabolic rate. The major cause for weight loss in most patients has been shown to be inadequate caloric intake. Anorexia is a common result of systemic infection and drug side effects. Patients with oropharyngeal and esophageal pathology have discomfort related to eating and will decrease intake. The presence of

gastrointestinal involvement is often associated with variable degrees of malabsorption so that the limited calories that are taken in are not assimilated efficiently. Increased basal metabolic rate as well as inefficient use of energy has been demonstrated in some cases. All of these contribute to weight loss.

Apart from treating the underlying infection there is no specific and effective therapy for wasting. With the new combinations of antiretroviral agents, patients have shown dramatic improvements, including weight gain and some reversal of wasting. Therefore, the control of HIV infection appears to be the most important factor in controlling wasting. Caloric intake should be optimized; the assistance of a dietitian is invaluable in helping patients in this regard. Intervention with enteral or parenteral nutritional support has not been generally effective, but may be used in selective cases.

6. CONCLUSIONS

Care of HIV-infected patients with gastrointestinal involvement represents a clinical challenge. Differential diagnosis and investigations should be guided by the degree of immunosuppression indicated by the CD4 lymphocyte count. As curative therapies for most of the GI problems are not available, therapy should be directed at effectively controlling the HIV infection with HAART and specific symptom relief of the GI symptoms. Functional status and psychosocial issues need to be considered for the successful management of these patients.