Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

42

GASTROINTESTINAL COMPLICATIONS OF SECONDARY IMMUNODEFICIENCY SYNDROMES

Tracie L. Miller • Laura L. Cushman

Secondary immunodeficiency syndromes constitute a spectrum of disorders. Infections of the gastrointestinal tract pose the greatest risk for children with secondary immunodeficiencies. Cellular changes in the gastrointestinal tract (the largest immune organ in the body) that lead to diarrhea and malabsorption, peptic disease, dysmotility, and liver disease are among some of the other disorders of the gastrointestinal tract faced by these children. Worldwide, human immunodeficiency virus (HIV-1) infection and malnutrition are by far the most common secondary immunodeficiency states. However, in the United States and other developed countries, severe malnutrition and new cases of perinatal HIV-1 disease are rare because of relatively high standards of living and effective highly active antiretroviral therapies (HAART) given to pregnant HIV-infected women that prevent transmission of HIV to the infants.[1] Between 2004 and 2005, there were 67 reported cases of perinatally acquired HIV and 4883 new diagnoses of unspecified origin in adolescents 13 to 24 years of age.[2] HIV-infected children and adolescents are now surviving because of effective antiretroviral strategies, yet there is increased horizontal acquisition of HIV in adolescents owing to risky social behaviors. Furthermore, children with chronic illness are among the highest population at risk for malnutrition and its sequelae.[3] Thus these two disorders serve as models for complications of other secondary immunodeficiency states.

PEDIATRIC HIV INFECTION

The first cases of the acquired immunodeficiency syndrome (AIDS) were described in the early 1980s. Later, in 1984,[4] HIV-1 was determined to be the causative agent, and HIV-1 infection was recognized as a spectrum of disease, ranging from asymptomatic infection to full-blown AIDS. The AIDS epidemic claimed an estimated 2 million lives in 2007, and an estimated 2.7 million people acquired HIV-1 in 2007. An estimated 33 million people globally are living with the virus.[5] With the successful preventive strategies of elective cesarean section delivery and chemoprophylaxis of pregnant HIV-1-infected women, the transmission rates plummeted from 15 to 30% to less than 1 to 2% of all HIV-1-infected women delivering infants.[6] The advent of HAART in 1996 changed the natural history of HIV-1 in children in many countries.[7] However, the successes of prevention and prophylaxis have not been realized as much in developing countries, where HIV infection continues to increase. For this reason, there are disparate accounts of opportunistic infections and other diseases in regions with high HAART accessibility and those with limited HAART accessibility.[8]

HIV-1 is an RNA virus that belongs to the lentivirus family. It has a particular tropism for the CD4 surface antigen of cells, and the binding of HIV-1 to the CD4 receptor initiates the viral cycle. The virus may subsequently replicate within the host cell or, alternatively, the proviral DNA within the host cells may remain latent until cellular activation occurs. Human T lymphocytes and monocytes-macrophages are the primary cells that are infected with HIV-1, although other cell lines may be infected as well. The net effect is suppression of the immune system and a progressive decline in CD4+ T lymphocytes, which leaves patients susceptible to opportunistic and recurrent bacterial infections.

HIV AND THE CELLULAR COMPONENTS OF THE GASTROINTESTINAL TRACT

The gastrointestinal tract is the main source of HIV-1 infection when parenteral transmission is excluded. In vertical transmission, HIV-1 is found in the gastrointestinal tract after the fetus swallows infected amniotic fluid, blood, cervical secretions, or breast milk. The virus, inoculated in the gastrointestinal tract, infects the fetus as it enters into the gut-associated lymphoid tissue (GALT) through the tonsil or upper intestinal tract. Examination of both acute simian immunodeficiency virus (SIV) and HIV infection have documented reduced CD4 cell levels in GALT prior to a detectable reduction in T cells of the peripheral blood, highlighting the gastrointestinal tract's role and susceptibility.[9-12] The rates of acquisition of HIV-1 through the gastrointestinal tract are likely related to the quantity of virus in the person transmitting it[13-15] and the immunologic function and maturity of the patient being infected. Mucosal infections with opportunistic infections may increase HIV-1 transmission. Mycobacterial infections up-regulate CC chemokine receptor 5 (CCR5) expression in monocytes, which facilitates the entry of CCR5-tropic HIV-1. Other factors, such as tumor necrosis factor-α (TNF-α), which is induced by nuclear factor (NF)-κB (which itself is pathogen induced), are potent inducers of HIV-1.[16,17]

Cellular routes that potentially can transmit HIV-1 across the gastrointestinal tract include M cells, dendritic cells, and epithelial cells. M cells are specialized epithelial cells that overlie the Peyer's patches and transport large macromolecules

and microorganisms from the apical surface to the basolateral surface. Human transport of HIV-1 by M cells in vivo has not been reported. Dendritic cells bind HIV-1 through a dendritic cell-specific adhesion molecule. In vitro studies support the role of dendritic cells in transmitting HIV-1[18-21]; however, the role of the dendritic cell in in vivo transmission of HIV-1 has yet to be determined. Epithelial cells express CCR5 and can selectively transfer CCR5-tropic HIV-1. The epithelial cell can transport HIV-1 in vitro from the apical to the basolateral surface.[22,23] The R5-tropic viruses are transferred in vitro through epithelial cell lines.[24]

Once transmitted, the lamina propria lymphocytes express CCR5 and CXC4 chemokine receptor 4 (CXCR4), which support HIV-1 replication.[25,26] Early after infection, there is a greater proportion of infected lymphocytes in the lamina propria than in peripheral blood.[27,28] For the patients actively receiving HAART, Poles et al.[29] described "cryptic replication" occurring in GALT reservoirs in which viral replication is actively taking place at slower rates but HIV-1 RNA levels remain undetected in peripheral blood. Further, GALT contained more than twice as many lymphoid cells (160,000) than peripheral blood mononuclear cells (70,000) possessing HIV-1 DNA with viral replication capacity. There was no significant reduction in these values when the analysis was repeated after 12 months. Lymphocytes are able to disseminate the virus to distant sites, with depletion of CD4 cells in the lamina propria[27,30] and then in the blood. Even with aggressive suppression of HIV-1 during the primary stages by highly active antiretroviral agents, CD4 cell depletion is observed in the effector subcompartment gut mucosa when CD4 levels in the peripheral blood have stabilized.[10] As mucosal and peripheral T cells are depleted, monocytes and macrophages become important reservoirs for the virus. The intestinal macrophages do not promote inflammation and do not carry the receptor for CCR5 or CXCR4; however, the blood monocytes are different in their profile and are infected by HIV-1. They are found infected in the blood and thereafter take up residence in the gut.[31] They are stimulated by opportunistic agents and proinflammatory cytokines.[32] Recent in vitro studies have implicated the integrin receptor $\alpha 4\beta 7$ on which the HIV-1 envelope binds and transmits signals mediated by an epitope in the V2loop of gp120. This in turn activates LFA-1 and is pivotal in virological synapse formation, allowing rapid cellular dissemination of HIV-1.[33]

Villous atrophy and gastrointestinal tract dysfunction are coincident with high levels of HIV-1 viral load in the gut.[34] Altered epithelial permeability may permit microbial translocation and generalized immune activation leading to localized cytokine production and further replication of HIV.[35] A dysfunctional gastrointestinal tract can produce clinical symptoms that contribute to both morbidity and mortality in children with HIV-1 infection. These symptoms include weight loss, vomiting, diarrhea, and malabsorption (Table 42-1). The advent of antiretroviral treatment induces debilitating effects on mechanisms within the gut that promote chronic HIV infection. Mainly, high levels of lipopolysaccharides (LPS) are associated with marked systemic immune activation sustaining this infection; antiretroviral therapy decreases levels of LPS, promotes CD4+ T cell reconstitution, and may subsequently decrease the systemic immune activation.[36] Additional studies examining this relationship stand to offer greater insight into HIV pathogenesis.

TABLE 42-1. **Gastrointestinal Symptoms and Causes in HIV-1-Infected Childre**

Anorexia, Nausea, Weight Loss, Vomiting	
Peptic disease	Idiopathic, gastroesophageal reflux, medications, *H. pylori*
Opportunistic infections of upper gastrointestinal tract	*Candida*, CMV, HSV
Pancreatic or hepatobiliary disease	Pancreatitis, cholangitis, infectious
Encephalopathy/CNS disorders	HIV
Idiopathic aphthous ulcers	HIV
Primary anorexia	HIV
Gastrointestinal dysmotility	HIV, autonomic, infectious, inflammatory
Medication toxicity	Specified in Table 3
Gastrointestinal Malabsorption, Diarrhea, Mucosal Disease	
Infectious	Bacterial, parasitic, viral
Inflammatory	HIV enteropathy, IBD
Disaccharidase deficiency	Infectious, inflammatory
Protein-losing enteropathy	Infectious, inflammatory
Fat malabsorption	Infectious, inflammatory
Hepatobiliary Disease	
Sclerosing cholangitis	Infectious
Chronic pancreatitis	Infectious, drug-induced
Cirrhosis	Hepatitis B and C co-infection

CMV, cytomegalovirus; CNS, central nervous system; HSV, herpes simplex virus; IBD, inflammatory bowel disease

STRUCTURE AND FUNCTION OF THE INTESTINAL TRACT IN HIV INFECTION

As mentioned, there are distinct changes in the cellular milieu of the gastrointestinal tract in HIV-1-infected patients. Previous studies have shown that activated mucosal T cells play a role in the pathogenesis of enteropathy in the human small intestine[37] and can affect the morphology of the villi and crypts in a manner similar to that seen in patients with HIV-1 infection. The magnitude of viral burden in the gastrointestinal tract is associated with villous blunting and other abnormal morphology.[34] A number of studies in the 1980s associated a distinct enteropathy with HIV-1.[38] Diarrhea, weight loss, an abnormally low D-xylose absorption, and steatorrhea, without evidence of intestinal infection, were common findings. Jejunal biopsies showed partial villous atrophy with crypt hyperplasia and increased numbers of intraepithelial lymphocytes. This was the first histologic description of a specific pathologic process that occurred in the lamina propria of the small intestine in some patients with HIV-1. Others[39] found low-grade small bowel atrophy and maturational defects of enterocytes, supporting an HIV-1 enteropathy characterized by mucosal atrophy with hyporegeneration. However, some investigators have challenged this concept, suggesting that the findings could be attributed to an undiagnosed enteric infection. Recently, genotype profiling for genes responsible for endothelial barrier maintenance and metabolic functioning has shown a decreased expression in the presence of increased viral replication in the GALT and reduced CD4+ T cell levels.[40] These findings are significant, because they offer an additional modality for evaluating microenvironmental alterations within the gastrointestinal

tract of the patient. Additional studies will help to determine the efficacy of gene expression profiling in HIV-infected individuals.

Miller et al.[41] published histologic findings in 43 children with HIV-1 infection. The majority of patients had normal villous architecture, and many of the children with villous blunting had an associated intercurrent enteric infection. Distinct features of hyperplasia of the lamina propria and increased intraepithelial lymphocytes were not apparent.

Bjarnason et al.[42] studied intestinal inflammation and ileal structure and function in patients with a wide spectrum of HIV-1 disease states. HIV-1-infected patients who were minimally symptomatic had normal intestinal absorption and permeability, yet had greater gastrointestinal dysfunction as they progressed to AIDS. Malabsorption of bile acids and vitamin B_{12} did not correlate with morphometric analysis of ileal biopsies and was unremarkable in these patients. Thus, there was significant mucosal dysfunction with only minor ileal morphologic changes. Malabsorption of bile acids may play a pathologic role in patients with AIDS diarrhea. The absorptive defect of AIDS enteropathy using a D-xylose kinetic model of proximal absorption was studied[43] and correlated with the results of a Schilling test for cobalamin absorption, which measures distal intestinal function. There were minimal histologic abnormalities in both the proximal and distal biopsy sites in patients with diarrhea and no enteric infection. D-Xylose absorption was low, and the absorptive defect was more severe and greater than would be expected from the histologic abnormalities found. Thus, these findings support the theory that there is little association between histologic characteristics of the small bowel and its absorptive function in patients with HIV-1 infection.

Most studies do not support a direct role for gastrointestinal malabsorption on growth failure or weight loss. Ullrich et al.[39] described gastrointestinal malabsorption in HIV-1-infected patients who had low levels of lactase enzyme in the brush border, crypt death, decreased villous surface area, and decreased mitotic figures per crypt when compared with control patients. In addition, Keating et al.[44] described absorptive capacity and intestinal permeability in HIV-1-infected patients. Malabsorption was prevalent in all groups of patients with AIDS, but was not as common in the asymptomatic HIV-1-infected patients. Malabsorption correlated with the degree of immune suppression and with body mass index. There were mild decreases in the ratio of jejunal villous height to crypt depth, yet not as severe as the subtotal villous atrophy found in celiac disease. Lim et al.[45] found disaccharidase activity decreased proportionately with greater HIV-1 disease severity, although there was no association between disaccharidase levels and weight loss. In addition, Mosavi et al.[46] found no correlation between diarrhea and weight loss in HIV-1-positive patients. Taylor et al.[47] found mild histologic changes accompanied by severe disaccharidase abnormalities; however, symptoms were severe enough to withdraw lactose in only 25% of the patients. Collectively these studies suggest that gastrointestinal malabsorption may be present, but is not always associated with weight loss and diarrhea.

Formal studies of intestinal absorption in children with HIV-1 are more limited. Malabsorption occurs frequently in HIV-1-infected children and may progress with the disease. In one study, 40% of children had nonphysiologic lactose malabsorption and 61% had generalized carbohydrate malabsorption that was not associated with gastrointestinal symptoms or nutritional status.[48] These findings have been confirmed by others.[49] Another study in children revealed an association between diarrhea and nutrition.[50] Abnormal D-xylose absorption has also been associated with enteric infections in children.[48] Fat and protein loss or malabsorption have also been described. Sentongo et al.[51] evaluated fat malabsorption and pancreatic exocrine insufficiency using fecal elastase-1 enzyme assay in 44 HIV-1-infected children. Hormone-stimulated pancreatic function testing and 72-hour stool and dietary fat sample collection were performed in children with abnormal fecal elastase levels. The prevalence of steatorrhea was 39% and that of pancreatic insufficiency was 0% (95% confidence interval 0 to 9%). There were no associations between steatorrhea and pancreatic insufficiency, growth, HIV-1 RNA viral load, CD4 status, or type of antiretroviral therapy. Other studies support the absence of association.[52] Thus, the clinical significance of steatorrhea in pediatric HIV-1, similar to absorption of other nutrients, is unclear.

The etiology of malabsorption in HIV-1 infection is probably multifactorial. The cellular milieu of the lamina propria is altered significantly with HIV-1 infection.[34,53] The depletion of the CD4 T lymphocytes in the intestinal tract may cause change in the cytokine environment and alter intestinal function. Viral load in the intestinal tract may be considerably higher than that measured peripherally, and this can also affect mucosal gastrointestinal structure and function. Recently, the HIV-1 Tat protein was found to decrease glucose absorption through decreasing the activity of the sodium D-glucose symporter.[54] Studies suggesting these hypotheses include that of Kotler et al.,[55] which looked at intestinal mucosal inflammation in 74 HIV-1-infected individuals. These authors found abnormal histopathology in 69% of the patients, and this finding was associated with altered bowel habits. High tissue P24 antigen levels were observed, and these correlated with more advanced HIV-1 disease. Tissue P24 detection was associated with both abnormal bowel habits and mucosal histology. The tissue content of cytokines, including TNF, α-interferon, and interleukin-1β, was higher in HIV-1-infected individuals than in controls, and these increases were independent of intestinal infection. Thus, HIV-1 reactivation in the intestinal mucosa could be associated with an inflammatory bowel-like syndrome in the absence of other enteric pathogens.

Small bowel bacterial overgrowth can be another source of gastrointestinal dysfunction leading to malabsorption. Bacterial overgrowth may be due to AIDS gastropathy,[56,57] in which the stomach produces only small amounts of hydrogen chloride, allowing bacterial pathogens to escape the acid barrier of the stomach and colonize the duodenum. Additionally, iatrogenic hypochlorhydria may be due to the use of acid-blocking agents as treatment for peptic disease. Interestingly, some authors have found no relationship between gastric pH and small bowel bacterial colonization and diarrhea in HIV-1-infected patients.[58] Enteric pathogens[59] have been associated with enteric dysfunction, as discussed later.

With the advent of HAART, gastrointestinal symptoms, especially those associated with opportunistic infections, are less common.[60] As viral burden decreases, immunosuppression has less effect on gastrointestinal function. Compared to untreated patients, HAART-treated patients had greater integrity of intestinal mucosal barrier and decreased villous atrophy.[61] Ritonavir, a protease inhibitor, in combination therapy resulted

in restoration of gastrointestinal function in 10 children with carbohydrate malabsorption, steatorrhea, protein loss, and iron deficiency.[62] However, one study in adults found similar rates of fat malabsorption in patients taking HAART and in those not taking HAART.[63]

INFECTIONS OF THE GASTROINTESTINAL TRACT

The gastrointestinal tract is a major target for opportunistic infections in HIV-1-infected children. The spectrum of these infections is dependent on HIV-1 disease progression. In developed countries, with improved HIV-1 viral suppression associated with HAART, opportunistic infections of the gut and elsewhere are less common.[64] However, immunocompromised children are still at risk for infections with cytomegalovirus (CMV), herpes simplex virus (HSV), *Cryptosporidium*, and microsporidia. Previous dogma that much of the diarrhea found in children with HIV-1 infection is not associated with enteric pathogens has been challenged. Unusual viral and parasitic infections can be diagnosed as a result of better diagnostic techniques. However, the cause of diarrhea in a significant number of patients with HIV-1 remains undiagnosed.[65]

Occurrence of opportunistic disease and infection of the gastrointestinal tract in immunocompromised patients relies heavily on the accessibility of HAART. As a result, there is great disparity of documented incidence of gastrointestinal infections dependent on access to HAART in particular regions. For this reason, we have divided this section into two subsections: gastrointestinal infections in regions with low HAART accessibility or in patients with CD4 T-lymphocyte counts less than 200 cells/mm^3, and gastrointestinal infections in regions with high HAART accessibility and successful viral suppression. This does not imply that any of the infections discussed here occur in isolation contingent on HAART accessibility, because all HIV-1 patients regardless of HAART may encounter these complications. In the post-HAART era, it is helpful for a physician to know which backdrop lends itself to specific vulnerabilities.

INFECTIONS OF THE GASTROINTESTINAL TRACT IN REGIONS WITH LOW HAART ACCESSIBILITY OR IN PATIENTS WITH CD4 COUNTS BELOW 200 CELLS/mm^3

Viral Infections

The detection of viral gastrointestinal infections in HIV-1-infected children can sometimes be difficult owing to the limitations of diagnostic techniques. The most common gastrointestinal viral pathogen in HIV-1-infected children is CMV. Other pathogens, such as HSV, adenovirus, Epstein-Barr virus, and a variety of other unusual viruses, can also contribute to intestinal dysfunction and diarrhea.

Herpes Simplex Virus

HSV infection in an immunocompromised child usually represents reactivation of a latent virus that had been acquired earlier in life. Gastrointestinal infection with HSV most commonly involves the esophagus and causes multiple small, discrete ulcers. HSV can also involve other areas of the intestinal tract, including the colon and small bowel. The diagnosis of HSV relies on recognizing the multinucleated intranuclear inclusion bodies (Cowdry type A) with a ground-glass appearance and molding of the nuclei. The squamous epithelium is usually infected, although there may also be involvement of intestinal glandular epithelium in the mesenchymal cells. HSV monoclonal antibody staining is confirmatory for the diagnosis. In extensive involvement, there may be transmural necrosis and development of tracheoesophageal fistulas. Treatment of HSV and other common gastrointestinal pathogens and their primary sites of involvement are outlined in Table 42-2.

Other herpes viruses have also been detected in the gut of HIV-1-infected individuals. A case report of one 34-year-old HIV-1-infected man with intestinal pseudo-obstruction and disseminated cutaneous herpes zoster revealed positive immunohistochemistry against herpes zoster in a resected portion of the terminal ileum. This area had focal ulceration. The virus was localized to the muscularis propria and myenteric plexi throughout the entire length of the specimen. The authors postulated that the location of the virus in the gut may have been the etiologic factor for the pseudo-obstruction.[66]

Cytomegalovirus

CMV in the immunocompromised child, like HSV, represents reactivation of a latent virus that was acquired in earlier life. CMV is one of the more common viral pathogens of HIV-1-infected children. The reported incidence of gastrointestinal involvement in the pre-HAART era varied from 4.4% to 52% of patients studied. The incidence rates may have varied based on the techniques of diagnosis.[57] CMV infection is rare in patients with CD4 T-lymphocyte counts greater than 50 cells/mm^3.[67] CMV may involve any part of the gastrointestinal tract, with an increased incidence in the esophagus or colon. CMV infection usually results in one or two discrete single and large ulcers of the esophagus and colon. Lesions may lead to severe gastrointestinal bleeding and hemodynamic instability. CMV inclusion bodies can be discovered incidentally in an asymptomatic patient, and this does not necessarily reflect disease.

In patients with upper intestinal CMV disease, there can be dysphagia and upper abdominal symptoms, whereas diarrhea is more common with colitis. The diarrhea can be watery or bloody. Children may be systemically ill.[68] The colitis from CMV infection is patchy and can be associated with severe necrotizing colitis and hemorrhage.[69] CMV usually affects the cecum and the right colon. Diagnosis is confirmed by endoscopy and biopsy. The histologic appearance of CMV-infected cells is unique (Figure 42-1). These cells are enlarged and contain intranuclear and cytoplasmic inclusion bodies. The nuclear inclusion bodies are acidophilic and are often surrounded by a halo. Cytoplasm inclusion bodies are multiple, granular, and often basophilic. Cells that are dying may appear smaller and smudged, with poorly defined inclusion bodies. Staining for CMV antigen shows that many of the infected cells are endothelial cells with others being perivascular mesenchymal cells. CMV can cause vasculitis because of its target cell population. Thus, the spread of CMV occurs with circulating infected endothelial cells. Treatment options are outlined in Table 42-2. Once HAART is established, with decreased viral burden (both HIV-1 and CMV) and improved CD4 counts, CMV treatment may be discontinued without concern for reactivation.[70]

TABLE 42-2. **Primary Location and Drug Therapy for Common Enteric Pathogens Infecting Immunocompromised Children**

Pathogen	Drug Treatment
Bacteria	
Salmonella (SI, C)	Ampicillin; TMP-SMZ; cefotaxime sodium, ceftriaxone sodium; fluoroquinolones (>18 years)
Shigella (SI, C)	Ampicillin, TMP-SMZ; ceftriaxone sodium; azithromycin; fluoroquinolones (>18 years)
Campylobacter (SI)	Erythromycin; azithromycin dihydrate; doxycycline (>8 years); fluoroquinolones (>18 years)
Yersinia (SI, C)	TMP-SMZ; tetracycline (>8 years); cefotaxime sodium; chloramphenicol; fluoroquinolones (>18 years)
Clostridium difficile (C)	Discontinue antibiotics, if possible; metronidazole; vancomycin; bacitracin; cholestyramine (may bind toxin and relieve symptoms); *Lactobacillus* GG
Mycobacteria	
Mycobacterium tuberculosis (SI)	Isoniazid; rifampin; pyrazinamide; ethambutol; aminoglycoside
MAC (SI)	(1) Clarithromycin or azithromycin combined with (2) ethambutol with adding (3) rifabutin (not in combination with PIs) or rifampin, plus (4) amikacin or streptomycin
Viruses	
Cytomegalovirus (SI, C)	Ganciclovir; foscarnet; CMV-IVIG; valganciclovir hydrochloride
Herpes simplex virus (O/P, E)	Aciclovir; foscarnet; famciclovir; penciclovir
Fungi	
Candida albicans (O/P, E)	Fluconazole, itraconazole, ketoconazole, amphotericin B
Histoplasma (SI)	Amphotericin B; fluconazole; itraconazole
Cryptococcus (SI)	Amphotericin B with oral flucytosine (serious systemic infections); fluconazole; itraconazole
Pneumocystis jiroveci (SI)	TMP-SMZ; pentamidine; atovaquone; dapsone
Parasites	
Cryptosporidia (SI)	Nitazoxanide; azithromycin; paromomycin, octreotide; human immune globulin; bovine hyperimmune colostrum
Microsporidia (SI)	Albendazole; metronidazole; atovaquone; nitazoxanide; fumagillin
Isospora belli (SI)	TMP-SMZ; pyrimethamine; fluoroquinolones (> 18 years)
Giardia lamblia (SI)	Metronidazole; furazolidone; nitazoxanide

C, colon; E, esophagus; MAC, *Mycobacterium avium-intracellulare* complex; O/P, oropharynx; PI, protease inhibitor; S, stomach; SI, small intestine; TMP-SMZ, trimethoprim-sulfamethoxazole.

Other Viral Infections

Infections with other unusual viral pathogens have been described. These include the human papilloma virus and Epstein-Barr virus, which have been identified in esophageal ulcers of patients with HIV-1. Adenovirus of the stomach and colon have also been reported and are often difficult to identify.[71] In the pre-HAART era, patients who excreted adenovirus from their gastrointestinal tract had a shorter survival.[72] There are unusual enteric viruses that have been associated with diarrhea in HIV-1-infected children.[73] These viruses, among others, include astrovirus and picobirnavirus.[74] Cegielski et al.[75] studied 59 children with HIV-1 infection in Tanzania. They looked for enteric viruses identified by electron microscopy of fecal specimens. Small round structured viruses (SRSVs) were found more frequently in HIV-1-infected children than in uninfected children with chronic diarrhea. Rotavirus and coronavirus-like particles were not associated with HIV-1 infection. These authors considered that these SRSVs may be associated with HIV-1 infection and could lead to chronic diarrhea in Tanzanian children.

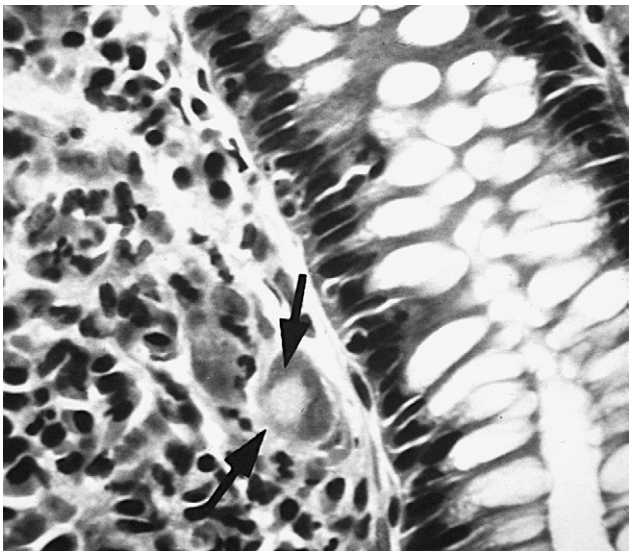

Figure 42-1. Small bowel biopsy showing cytomegalovirus inclusion (arrows) within the lamina propria.

Bacterial Infections

Bacterial infections that involve the gastrointestinal tract of children with HIV-1 infection may be divided into three groups: bacterial overgrowth of normal gut flora; pathogens that can affect immunocompromised children as well as immunocompetent children (*Salmonella*, *Shigella*, *Campylobacter*, *Clostridium difficile*, and *Aeromonas*); and bacterial infections that are more common in immunocompromised children (*Mycobacterium avium-intracellulare* complex; MAC).

Few studies have evaluated bacterial overgrowth in HIV-1-infected children, although gastric hypoacidity has been associated with opportunistic enteric infections and bacterial overgrowth in adult patients with HIV-1.[76] Other studies have not found this association. Small bowel bacterial overgrowth was not a common finding in a group of 32 HIV-1-infected patients, regardless of the presence of diarrhea, and it was not associated with hypochlorhydria.[58] Lactose hydrogen breath testing has shown high baseline readings in children that may indirectly suggest bacterial overgrowth of the small intestinal tract.[48] Detection of bacterial overgrowth in the small bowel is usually performed by quantitative duodenal aspirate for bacterial culture, with therapy directed at treating the organisms, which are often anaerobic.

Common Bacterial Infections

Common bacterial pathogens include *Salmonella*, *Shigella*, *Campylobacter*, *Clostridium difficile*, and *Aeromonas*. Infection with these organisms occurs more frequently in immunocompromised patients. Combined morbidity and mortality rates associated with HIV-1 and these bacterial pathogens in developing countries approach 50% in some studies.[77] HIV-1-infected patients with *Campylobacter* infection have higher rates of bacteremia than the general population. Deaths from sepsis due to this organism have been reported in severely immunodeficient patients with AIDS, despite HAART.[78]

Escherichia coli

Other entities, such as bacterial enteritis, have been described in adults with HIV-1. A study by Orenstein and Kotler[79] evaluated ileal and colonic biopsies in patients with AIDS and diarrhea and found bacteria similar to adherent *E. coli* along the intestinal epithelial border. Similar findings were documented by Kotler et al.,[80] who showed adherent bacteria in 17% of all adult patients with AIDS. The infection was localized primarily to the cecum and right colon, and three distinct histopathologic patterns of adherence were observed: attachment on effacing lesions, bacteria intercalated between microvilli, and aggregates of bacteria more loosely attached to the damaged epithelium. The bacterial cultures of frozen rectal biopsies yielded *E. coli* in 12 of the 18 patients. These findings suggest that chronic infection with adherent bacteria can also produce the syndrome of AIDS-associated diarrhea. In a "look back" evaluation, Orenstein and Dieterich[71] found that enteropathogenic bacterial infections were overlooked on initial examination and concluded that, for accurate diagnoses, specimens should be evaluated by laboratories with expertise in HIV.

Mycobacteria

Intestinal infections with mycobacteria, including *Mycobacterium tuberculosis*, MAC, and other atypical mycobacteria, were the most frequently encountered bacterial infections in HIV-1-infected patients in the pre-HAART era[81] and became more prevalent in the pre-HAART era as patients were living longer with CD4 counts below 200 cells/mm^3.[82,83] In the HAART era, disseminated MAC in colonized patients can be successfully prevented; however, the effects of HAART on restoration of CD4 counts do not prevent MAC colonization.[84]

Infection with MAC usually occurs in the very late stages of AIDS in children, when CD4 counts are lower than 200 cells/mm^3. The most common clinical manifestations of gastrointestinal infections with MAC include fever, weight loss, malabsorption, and diarrhea. Intestinal obstruction, resulting from lymph node involvement and intussusception; terminal ileitis, which resembles Crohn's disease; and refractory gastric ulcers are often found. Severe gastrointestinal hemorrhage has also been described.[85] Endoscopically, fine white nodules may be seen in the duodenum, or the duodenal mucosa may look velvety and grayish in appearance. Segments of the gastrointestinal tract can become infected with MAC. Histologically, there is a diffuse histiocytic infiltrate in the lamina propria with blunting of the small intestinal villi. These histiocytic infiltrates can be recognized on hematoxylin and eosin staining and on acid-fast stains and are pathognomonic for infection (Figure 42-2). With the advent of HAART, immune reconstitution disease has been described.[86,87] This is likely an immune reaction in which previously quiescent organisms become active because of the improved immune function associated with HAART. This can occur in as many as 25% of patients who respond to HAART.[88] Lymphadenitis is the most common condition, although abscesses can appear anywhere. Severe abdominal complaints may result.

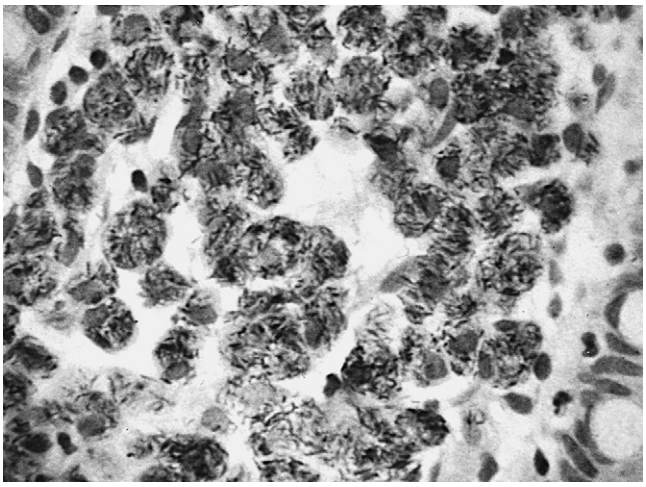

Figure 42-2. Small bowel biopsy showing histiocytes infiltrated with *Mycobacterium avium-intracellulare* within the lamina propria.

Appropriate therapies are outlined in Table 42-2, yet this organism is often frustrating to treat. Azithromycin 600 mg, when given in combination with ethambutol, is an effective agent for the treatment of disseminated *M. avium* disease in patients infected with HIV-1.[89] Caution must be exercised in administering these multidrug regimens for MAC in patients receiving concurrent HAART. Rifamycins induce cytochrome P450 enzymes and accelerate the metabolism of clarithromycin and HIV-1 protease inhibitors. Conversely, clarithromycin inhibits these enzymes, resulting in increased rifabutin toxicity. The net result is treatment regimens that can be extremely difficult to tolerate and manage, especially for sicker patients. Clarithromycin and azithromycin must be administered in combination with other agents, such as ethambutol, to prevent the emergence of macrolide resistance.[90]

Parasitic infections

Cryptosporidium parvum

In the early 1980s, cryptosporidiosis was regarded as an AIDS-defining disease and an opportunistic intestinal pathogen. It became an important cause of chronic diarrhea, leading to high morbidity and mortality rates in immunocompromised patients. To date, no effective chemotherapy is available. With the introduction of protease inhibitors in HAART regimens, the incidence of cryptosporidiosis in patients with AIDS has declined substantially in developed countries.[91] However, in developing nations, gastrointestinal infection with *C. parvum* is prevalent and carries high morbidity and mortality rates.[92,93]

Although *Cryptosporidium* was initially described in animals, it was first noted to cause an enterocolitis in both immunocompromised and immunocompetent humans in 1976.[94,95] An intact T-cell response is the primary mechanism that confers protection against this organism; thus, patients with abnormal T-cell function or number are at risk. The spectrum and severity of disease in immunocompromised individuals with cryptosporidiosis correlates with most severe disease found in individuals with defects in the T-cell response.[91] The overall frequency of

infection seems to be related to the severity of immunodeficiency and not the specific disorder.[96]

Cryptosporidium usually affects the gastrointestinal tract, although it has been found in other organs including the biliary tract,[97] pancreas,[98] and respiratory tract.[99] In immunocompetent individuals, the diarrhea is self-limiting, whereas in immunocompromised patients, it may be protracted and associated with significant malabsorption and nutritional compromise. The small intestine is the primary target, although it can occur in any part of the intestinal tract. Esophageal cryptosporidiosis has also been described in one child[100] and in adults. Clayton et al.[101] described two patterns of enteric cryptosporidiosis. One was accompanied by severe clinical disease with significant malabsorption, with the majority of the organisms found in the proximal small bowel, whereas less severe clinical disease was seen in patients with colonic disease or with infection noted only in the stool. Patients with proximal small bowel infection with *Cryptosporidium* showed crypt hyperplasia, villous atrophy, lamina propria inflammatory infiltrates, abnormal D-xylose absorption, greater weight loss, and shorter survival, with greater need for intravenous hydration and hyperalimentation than patients with colonic disease. In other studies, absorption of nutrients showed an inverse correlation with active infection,[102] as shown by altered vitamin B_{12} and D-xylose absorption and lactulose and mannitol urinary excretion ratios. Intestinal function improved in patients whose oocyte counts were reduced by treatment with paromomycin.

Symptomatic cryptosporidiosis has been documented in as many as 6.4% of immunocompetent children and 22% of immunodeficient children, whereas in an asymptomatic population, *Cryptosporidium* was found in 4.4% of immunocompetent and 4.8% of immunodeficient children.[103] Spiramycin at 100 mg per kg daily for 14 days caused a significant reduction in the shedding of infectious oocysts, and no gastrointestinal symptoms developed in children treated for asymptomatic infection, whereas children who were not treated developed gastrointestinal symptoms.[103]

The diagnosis of cryptosporidiosis is made by identifying the organisms in a duodenal aspirate, stool, or tissue sample (biopsies). On hematoxylin and eosin-stained sections, these organisms can be found as rows or clusters of basophilic spherical structures 2 to 4 μm in diameter, attached to the microvillous border of the epithelial cells (Figure 42-3). The tips in the lateral aspect of the villi show the greatest number of organisms in the small intestine. In the colonic epithelium, the crypt and surface epithelial involvement appears equal. *Cryptosporidium* also stain positively with Giemsa and negatively with mucous stains. The acid-fast stain on a stool sample is one of the most widely used methods of determining whether a patient has cryptosporidiosis. More recent sensitive and specific methods for diagnosing cryptosporidiosis include fluorescein-labeled IgG monoclonal antibodies.[104,105]

Treatment of cryptosporidiosis in children with HIV-1 infection is often difficult. The disease can be chronic and protracted with diffuse watery diarrhea and dehydration. Several different agents are used to eradicate the organism, with varying success rates. The most effective treatment is to improve immunologic function and nutritional status. With the advent of HAART, many children's immune function has been restored with a lower incidence and prevalence of *Cryptosporidium* infection.[106] The introduction of HAART in a patient with severe debilitating *Cryptosporidium* infection not only resulted in an increased CD4 count in the peripheral blood and clearance of the organism, but also produced a marked increase in CD4 count in the rectal mucosa on biopsy, suggesting this may have been the main mechanism of clearing the parasite.[107] Octreotide therapy of acute and chronic diarrhea, with coincident improvement in nutritional status, eradicated *Cryptosporidium* in one patient.[105,108] Other investigators have used bovine hyperimmune colostrum with benefit.[109,110] The macrolides, such as azithromycin, have shown some promise in the treatment of *Cryptosporidium* infection.[111,112] The effect of protease inhibitors as therapy against *Cryptosporidium* has been tested in a cell culture system.[113] Nelfinavir moderately inhibited the host cell invasion over a period of 2 hours. Indinavir, nelfinavir, and ritonavir inhibited parasite development significantly. The inhibitory effect was increased when the aminoglycoside paromomycin was combined with the protease inhibitors indinavir, ritonavir and, to a lesser extent, saquinavir, compared with the protease inhibitor alone. Thus, protease inhibitor therapy may directly (rather than indirectly, through its effects on the immune system) inhibit growth of *Cryptosporidium*. Amadi et al.[92] found that a 3-day course of nitazoxanide improved diarrhea, helped eradicate the parasite, and improved mortality in HIV-1-seronegative, but not HIV-1-seropositive, children in Zambia. Treatment with nitazoxanide on immunocompetent patients demonstrated parasitic load reduction, but its effects on immunocompromised patients are not yet palpable.[114]

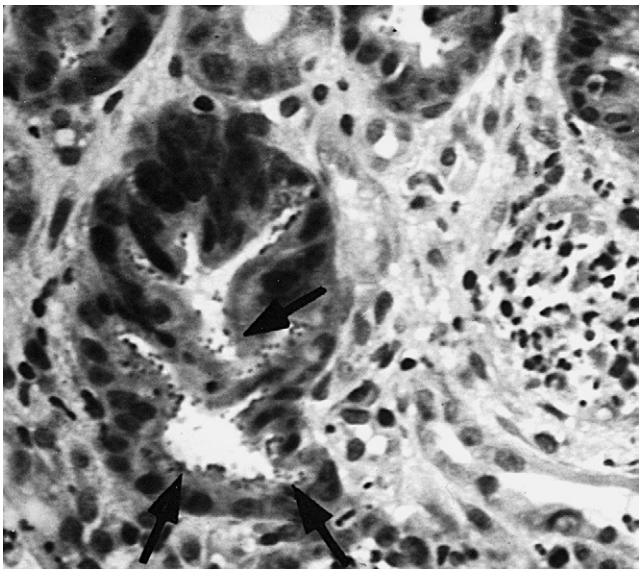

Figure 42-3. Small bowel biopsy showing *Cryptosporidium* attached to the villus (arrows).

Microsporidia

Microsporidia are obligate intracellular protozoal parasites that infect a variety of cell types in many different species of animals. These organisms were first described in 1857, when recognized as a cause of disease in nonhuman hosts.[115] The first description of microsporidia (*Enterocytozoon bieneusi*) as a human pathogen was in 1985, and microsporidia have since been described as more common human pathogens.[116] Infection with microsporidia typically occurs in patients with severely depressed CD4 T-lymphocyte counts. One of the largest case studies of intestinal microsporidiosis in patients with HIV-1 infection was

described by Orenstein et al.[117] in 67 adult patients with AIDS and AIDS-related complex and chronic nonpathogenic diarrhea. *E. bieneusi* was diagnosed by electron microscopy in 20 of the patients. Jejunal biopsies were more positive than duodenal biopsies. The parasites and spores were clearly visible by light microscopy in 17 of the 21 biopsies. Infection was confined to enterocytes located at the tip of the intestinal villus, and the histologic findings included villous atrophy, cell degeneration, necrosis, and sloughing. Other investigators[118-120] found microsporidia in as many as 50% of HIV-1-infected patients with chronic and unexplained diarrhea evaluated in the pre-HAART era. *E. bieneusi* has been documented in 15 to 25% of children with[121] or without[122] diarrhea in developing countries, making it fairly ubiquitous in these regions of the world. Other species of microsporidia, including *Encephalitozoon (Septata) intestinalis*, can cause significant enteric disease with diarrhea, wasting and malabsorption. *Encephalitozoon intestinalis* differs from *Enterocytozoon bieneusi* in its tendency to disseminate, and it can infect enterocytes as well as macrophages, fibroblasts, and endothelial cells.

Microsporidia are found with increasing frequency in HIV-1-negative patients.[123] Infection has been documented in almost every tissue and organ in the body, and in epithelial, mesenchymal, and neural cells. Microsporidia can cause inflammation and cell death and a variety of symptoms including shortness of breath, sinusitis, and diarrhea with wasting. If left untreated, microsporidiosis can be a significant cause of mortality.

Treatments for microsporidia include albendazole, which can relieve clinical symptoms and eliminate microsporidial spores in the feces, especially of the less common pathogen, *E. intestinalis*. *E. bieneusi* is more challenging to treat, although therapy with fumagillin or its analogue, TNP-470 (antiangiogenesis agents), has shown promising results.[124-126] Other studies show atovaquone as an effective treatment as well.[127] Indirect treatment by improving the immune system with HAART has also effectively cleared these organisms.[106,128,129]

Isospora belli

Isospora belli is recognized as an opportunistic small bowel pathogen in patients with HIV-1 infection. This organism is most common in tropical and subtropical climates. Isosporiasis can be diagnosed by identification of the oocyte in the stool or by biopsy. The diagnosis is critical because, in contrast to cryptosporidiosis or microsporidiosis, the therapy is very effective. *I. belli* is found within the enterocyte and within the cytoplasm. The organism stains poorly, although the central nucleus, large nucleolus, and perinuclear halo give it a characteristic appearance. The infection produces mucosal atrophy and tissue eosinophilia. A 10-day course of trimethoprim-sulfamethoxazole is effective therapy, and recurrent disease can be prevented by ongoing prophylaxis with this combination drug.[130] Ciprofloxacin, although not as effective, is an acceptable alternative for those with sulfa allergies.[130] Other therapies for *Isospora* include pyrimethamine, also indicated for patients with sulfa allergies.[131]

Other Parasites

Blastocystis hominis is usually considered a nonpathologic parasite, but it has been described in patients with chronic diarrhea and HIV-1 infection.[132] This organism is more pathogenic in immunocompromised patients and can cause mild, prolonged, or recurrent diarrhea. Effective therapy includes diiodohydroxyquinoline 650 mg orally three times daily for 21 days. Other protozoan infections that can be found in HIV-1-infected patients are *Entamoeba histolytica*, *Entamoeba coli*, *Entamoeba hartmanni*, *Endolimax nana*, and *Giardia lamblia* in 4% of cases.

Fungal Infections

Candida albicans

Candidiasis of the gastrointestinal tract is the most common fungal infection in HIV-1-infected children. The esophagus is the primary target of *Candida*, and this infection occurred in the majority of patients during the course of their illness in the pre-HAART era. It was also the second most frequent AIDS-defining disease, second in prevalence only to *Pneumocystis jirovecii*. Patients with *Candida* esophagitis complain of odynophagia or dysphagia and may often have vomiting and recurrent abdominal pain. Children often have oral thrush, coincident with more disseminated and invasive *Candida* esophagitis, although the absence of oral thrush does not preclude the diagnosis of *Candida* esophagitis.[41] In one study, oral candidiasis preceded the diagnosis of *Candida* esophagitis in 94% of children.[133] Other risk factors include low CD4 count and prior antibiotic use.[133] Histopathologically, yeast forms within an intact mucosa confirm invasive disease. This is in contrast to colonization, where the yeast is found overlying intact mucosal surfaces or necrotic tissue. These organisms are best seen with Grocott's methenamine silver method or periodic acid-Schiff stain. Upper gastrointestinal studies are suggestive of *Candida* esophagitis with diffuse mucosal irregularities (Figure 42-4). Upper gastrointestinal endoscopy with biopsy and appropriate staining is the most sensitive test for determining invasive candidiasis of the esophagus. Candidiasis can also occur in the stomach, as well as the small bowel if the acid barrier has been suppressed either through an intrinsic decrease in gastric acid production or iatrogenically with the use of potent acid blockers. Numerous effective therapies have been described to treat *Candida* of the upper gastrointestinal tract, including fluconazole, ketoconazole, and itraconazole.[134,135] Ketoconazole has more hepatic side effects than fluconazole. Itraconazole is usually well tolerated and is effective. In severe and invasive disease, either topical or intravenous amphotericin can be used. Agents such as oral miconazole and nystatin are not indicated for invasive *Candida*.

Other Fungal Infections

Disseminated histoplasmosis develops in 5% of adult patients with AIDS in the Midwestern region of the United States, and elsewhere. The clinical signs and symptoms related to this infection may be indolent, but left untreated can carry significant morbidity and mortality.[136] The likelihood of disease is higher in patients with CD4 counts under 200 cells/mm^3.[137] There is enterocolitis associated with infection, and at colonoscopy, plaques, ulcers, pseudopolyps, and skip areas are frequently seen. Cryptococcal gastrointestinal disease has been identified in patients with disseminated *Cryptococcus* infection. The esophagus and colon are involved most frequently. *P. jirovecii* infection of the gastrointestinal tract has also been described.[59] Gastrointestinal pneumocystosis develops after hematogenous or lymphatic dissemination from the lungs, or reactivation of latent gastrointestinal infection. The administration of aerosolized pentamidine has increased the risk of

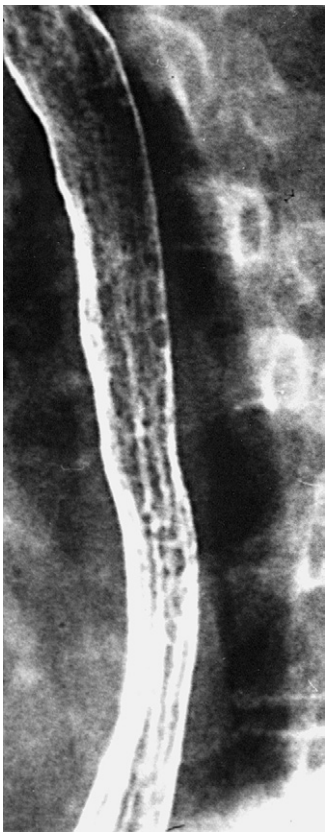

Figure 42-4. Radiographic contrast study showing mucosal irregularities seen with *Candida* esophagitis.

developing extrapulmonary spread of *P. jirovecii* pneumonia. *P. jirovecii* pneumonia infection can occur throughout the gastrointestinal tract. In the lamina propria there are foamy exudates with *P. jirovecii* organisms found within them. Although more rare, infection of the colon can also cause diarrhea.

INFECTIONS OF THE GASTROINTESTINAL TRACT IN REGIONS WITH HIGH HAART ACCESSIBILITY AND SUCCESSFUL HIV VIRAL SUPPRESSION

The effect of HAART on rates of infection of the gastrointestinal tract are twofold. First, on a macro level, the advent of HAART has led to a dramatic decrease in perinatal transmission of HIV, and therefore the rates of newly infected children have plummeted,[138] with reports of vertical transmission falling between 1 and 2%.[139] Second, HAART has been successful in immune reconstitution, and therefore in regions with high HAART accessibility, there has been a marked decrease in the number of HIV patients presenting with opportunistic infections. These infections have not been eradicated, but the majority of patients adhering to HAART are able to achieve CD4+ cell reconstitution and therefore stave these off. Patients who sustain chronically low CD4+ T lymphocyte levels in spite of HAART accessibility and usage continue to be at risk for the opportunistic infections[140] described in the previous section. When comparing incidence rates of opportunistic infection in the pre- (before January 1, 1997) and post-HAART era, there was an overall decrease.[8,141] Specifically: incidence rates of CMV decreased from 1.4 to 0.1; esophageal candidiasis from 0.9 to 0.4; herpes simplex virus from 0.2 to 0; and chronic intestinal and cryptosporidiosis from 1.3 to 0 per 100 persons per year.[141] Additionally, Nachman et al.[142] reported successful withdrawal of opportunistic infection prophylaxis for a period of 132 weeks in pediatric HIV-positive patients more than 2 years old who had achieved CD4 reconstitution without significant incidence when compared to demographically matched HIV-negative patients. In light of this progress, we have integrated additional immunocompromised patient populations into our discussion of gastrointestinal vulnerabilities.

Bacterial Infections

Clostridium difficile

Colitis from *C. difficile* is also more common in the immunosuppressed population owing to chronic antibiotic use and impaired immune system.[143] Pulvirenti et al.[144] studied 161 HIV-1-infected patients with *C. difficile* and found that they had longer hospital stays and more admissions than patients without *C. difficile* infection, as well as other opportunistic infections such as herpes virus. They found *C. difficile*–associated diarrhea in 32% of all study patients with diarrhea. However, infection with *C. difficile* appeared to have little impact on morbidity or mortality. In a 1998, New York state screening study[145] of hospitalized HIV-1-infected patients in the HAART era, 2.8% were admitted with a diarrheal diagnosis, with 51.3% of these having a *C. difficile* infection. Thus, even with HAART, diarrhea is prevalent and is often associated with identifiable pathogens. *C. difficile* infection has been reported to be one of the most common bacterial diarrheal pathogens among HIV-infected patients although its rates have decreased with HAART.[146] Because of the serious complications that are associated with active bacterial enteric infections in immunodeficient children, treatment options are outlined in Table 42-2.

Helicobacter pylori

H. pylori prevalence is not significantly different between HIV-1-infected patients and HIV-1-negative patients.[147,148] Some investigators have found the seroprevalence of *H. pylori* to be lower in HIV-1-infected patients,[149] especially as CD4 counts decline with advancing disease.[147] The protection from *H. pylori* may be a result of frequent antibiotic use or correlated with a more advanced, dysfunctional immune state that results in a decreased inflammatory response to the organism.[150] Remission of a high-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma followed *H. pylori* eradication and HAART in a patient with AIDS.[151] However, a recent study of HIV-infected adults showed that 32% of patients with peptic symptoms had *H. pylori* on biopsy, with those having CD4 counts above 200 cells/mm^3 at a higher risk.[152] Treatment of *H. pylori* in HIV-1-infected children is similar to that in noninfected children, with special attention to drug interactions.

MOTILITY OF THE GASTROINTESTINAL TRACT IN HIV INFECTION

In up to 15 to 25% of HIV-1-infected children, the etiology of the diarrhea is unclear. Autonomic dysfunction is another potential mechanism of noninfectious diarrhea not previously described. Clinically, children with autonomic neuropathy have sweating, urinary retention, and abnormal cardiovascular

hemodynamics. It is possible that this autonomic denervation contributes to diarrhea in patients with HIV-1 infection, as suggested by Griffin et al.[153] When neuron-specific polyclonal antibodies were applied to jejunal biopsies, there was a significant reduction in axonal density in both villi and pericryptal lamina propria in patients with HIV-1 infection compared with controls, with the greatest reduction in patients with diarrhea. Octreotide therapy has shown promising results in some patients.[154] Finally, drug side effects should be considered, with many of the antiretroviral therapies causing chronic diarrhea and other gastrointestinal toxicities (Table 42-3).

Motility problems of the esophagus and stomach have been reported[155-157] and can be a source of upper gastrointestinal complaints including vomiting, dysphagia, nausea, and dyspepsia. The motility abnormalities may be primary, or they may be secondary to infectious or inflammatory disease of the respective organ. Hypertension of the lower esophageal sphincter with incomplete relaxation, esophageal hypocontraction, and nonspecific motility disorders have been described in patients with normal intact esophageal mucosa.[156] Gastric emptying, especially in patients with infections or advanced disease, may be delayed, as documented by gastric scintigraphy.[155] However, delayed gastric emptying does not always correlate with upper gastrointestinal symptoms or small bowel motility studies. In adults with HIV-1 infection and minimally advanced disease, gastric emptying of solids was delayed and emptying of liquids accelerated compared with that in controls. No abnormal esophageal motility patterns were found. All patients had

TABLE 42-3. **HIV-Related Medications and Common Gastrointestinal Side Effects**

Medication	Action	Side Effects
Abacavir	NRTI	Nausea, vomiting, abdominal pain, pancreatitis, abnormal liver function
Aciclovir	Antiviral	Nausea, abdominal pain, diarrhea, abnormal liver function
Amprenavir	PI	Abdominal pain, diarrhea
Atazanavir	PI	Nausea, diarrhea, abdominal pain, hyperbilirubinemia
Atripla (tenofovir, emtricitabine, efavirenz)	Combination	Nausea, vomiting, diarrhea, abdominal pain, hepatitis, bone loss, pancreatitis, lactic acidosis
Azithromycin	Antibacterial	Nausea, vomiting, melena, jaundice
Ciprofloxacin	Antibacterial	Ileus, jaundice, bleeding, diarrhea, anorexia, oral ulcers, hepatitis, pancreatitis, vomiting, abdominal pain
Clarithromycin	Antibacterial	Nausea, diarrhea, abdominal pain, abnormal taste
Combivir (zidovudine-lamivudine)	Combination	Nausea, vomiting, abdominal pain, abnormal liver function, pancreatitis, lactic acidosis
Darunavir	PI	Nausea, vomiting, diarrhea, abdominal pain, pancreatitis, hepatitis, constipation
Didanosine (ddI)	NRTI	Nausea, vomiting, abdominal pain, pancreatitis, abnormal liver function
Efavirenz	NNRTI	Nausea, vomiting, abnormal liver function
Emtricitabine	NRTI	Lactic acidosis, hepatomegaly
Epzicom (zidovudine, abacavir)	Combination	Nausea, vomiting, abdominal pain, abnormal liver function, lactic acidosis, pancreatitis
Erythromycin	Antibacterial	Nausea, vomiting, abdominal pain
Etravirine	NNRTI	Nausea, vomiting, diarrhea, abdominal pain, hepatitis
Fosamprenavir	PI	Nausea, diarrhea, vomiting, abdominal pain
Enfuvirtide (Fuzeon)	FI	Nausea, diarrhea, abdominal pain, hepatitis, pancreatitis, dry mouth, anorexia
Ganciclovir	Antiviral	Nausea, vomiting, diarrhea, anorexia, abnormal liver function
Indinavir	PI	Nausea, vomiting, abdominal pain, diarrhea, changes in taste, jaundice, abnormal liver function
Ketoconazole	Antifungal	Hepatotoxicity
Lamivudine (3TC)	NRTI	Nausea, diarrhea, vomiting, abdominal pain, pancreatitis, abnormal liver function
Lopinavir/ritonavir	PI	Diarrhea, nausea, abdominal pain
Maraviroc	FI	Nausea, constipation, diarrhea, flatulence, abdominal pain, hepatitis, dysgeusia, stomatitis
Nelfinavir	PI	Nausea, diarrhea, fatigue, abnormal liver function
Nevirapine	NNRTI	Stomatitis, nausea, abdominal pain, raised gamma-glutamyl transpeptidase level, hepatotoxicity
Pentamidine	Antiparasitic	Abdominal pain, bleeding, hepatitis, pancreatitis, nausea, vomiting
Raltegravir	II	Gastritis, hepatitis, nausea, hyperbilirubinemia
Rifampin	Antibacterial	Abdominal pain, nausea, vomiting, diarrhea, jaundice
Ritonavir	PI	Nausea, vomiting, diarrhea, abdominal pain, pancreatitis, abnormal liver function
Saquinavir	PI	Mouth ulcers, nausea, abdominal pain, diarrhea, pancreatitis, abnormal liver function
Stavudine (d4T)	NRTI	Nausea, vomiting, abdominal pain, diarrhea, pancreatitis, abnormal liver function, hepatic failure
Sulfonamides	Antibacterial	Hepatitis, pancreatitis, stomatitis, nausea, vomiting, abdominal pain
Tenofovir	NRTI	Nausea, vomiting, diarrhea, abdominal pain, hepatitis, bone loss, pancreatitis
Tipranavir	PI	Hyperlipidemia, nausea, vomiting, diarrhea, abdominal pain, pancreatitis, hepatitis
Trizivir (abacavir-lamivudine-zidovudine)	Combination	Nausea, vomiting, abdominal pain, pancreatitis, abnormal liver function
Truvada (emtricitabine, tenofovir)	Combination	Lactic acidosis, nausea, vomiting, diarrhea, abdominal pain, hepatitis, bone loss, pancreatitis
Zalcitabine	NRTI	Pancreatitis, hepatic failure (with HBV), steatosis, lactic acidosis
Zidovudine (ZDV)	NRTI	Nausea, vomiting, abdominal pain, abnormal liver function

FI, fusion inhibitor; HBV, hepatitis B virus; II, integrase inhibitor; NNRTI, nonnucleoside–reverse transcriptase inhibitor; NRTI, nucleoside analogue–reverse transcriptase inhibitor; PI, protease inhibitor.

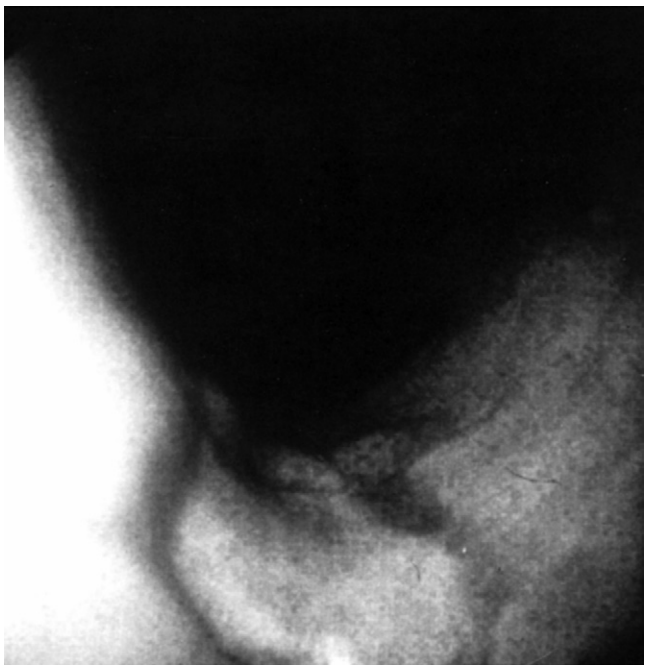

Figure 42-5. Endoscopic view of the esophagus in an HIV-infected child with a large idiopathic esophageal ulcer.

a normal endoscopy prior to the motility studies.[157] Thus, in the absence of infectious and inflammatory disease in patients with appropriate symptoms, motility studies or empiric trials of prokinetic agents should be considered, with careful consideration of drug interactions.

IDIOPATHIC ESOPHAGEAL ULCERATION

Esophageal ulceration can be a result of an intercurrent opportunistic infection. Idiopathic oral and esophageal ulcers have been described in both children and adults with HIV-1.[158] These ulcers are characteristically large and may be single or multiple (Figure 42-5). The ulcers are located in the mid to distal esophagus. Controversy exists regarding the pathogenesis of these ulcers; some investigators have identified HIV-1 at the ulcer base,[159] whereas others have not.[160] Treatment options for these ulcers are limited, but include steroid therapy, with encouraging results,[159] and thalidomide.[161,162] However, chronic low-dose thalidomide does not prevent recurrence of the oral or esophageal aphthous ulcers.[163] In addition to the potentially teratogenic effects, a significant portion of children receiving thalidomide develop a rash, which precludes use of the drug. Significant caution should be exercised when using thalidomide. Overall, HAART has had a positive impact on esophageal disease occurrence and relapse.[164]

CLINICAL MANAGEMENT OF GASTROINTESTINAL DISORDERS IN HIV INFECTION AND OTHER IMMUNODEFICIENCIES

The diagnostic approach to the child with HIV-1 or other immunodeficiencies and gastrointestinal symptoms is outlined in Table 42-4. A comprehensive clinical history should be taken with a focus on estimating caloric intake and evaluating abdominal symptoms, such as diarrhea, vomiting, and abdominal pain. Growth history should also be reviewed. The physical examination should focus on an assessment of nutritional state and the possibility of intestinal or hepatobiliary disease. With diarrheal symptoms, every HIV-1-infected child should have a complete evaluation for bowel pathogens. This should precede all other diagnostic studies, as treatment of the pathogen may result in resolution of the symptoms. Investigation for enteric infections should include studies for the organisms outlined in the preceding section on infectious diarrhea. The child's antiretroviral regimen and initiation of new medications should be noted as many of these medications produce significant gastrointestinal side effects (see Table 42-2). Every effort should be made to correlate timing of the initiation of a drug with onset of symptoms. The clinician should keep in mind that children with active enteric infections may also have secondary problems with malabsorption.

If the clinical history and physical examination are suspicious for malabsorption without enteric infection, the next step should include an evaluation of specific nutrient absorption. Carbohydrate malabsorption can be detected through lactose breath hydrogen testing, which measures hydrogen production as a response to an oral lactose load. A raised baseline breath hydrogen or early peak of hydrogen production suggests bacterial overgrowth, and appropriate treatment can be initiated. Lactose malabsorption results in a level of hydrogen production more than 10 to 15 parts per million over baseline, 60 minutes after ingestion. Dietary changes can then be made.

D-Xylose absorption testing also helps to determine the absorptive capacity of the gastrointestinal tract. D-Xylose is

TABLE 42-4. **Approach to Diagnosis of Gastrointestinal Tract Disease in the Immunocompromised Child**

Preliminary Evaluation

1. Complete history and physical examination
   Caloric intake, anthropometrics, gastrointestinal symptoms
   Drug interactions
   Oropharyngeal, abdominal, and rectal examinations
2. Laboratory
   Complete blood count, viral load (if chronic viral infection), immune function, chemistries (liver function studies, lactate dehydrogenase, pancreatic studies)
3. Evaluation for enteric pathogens
   Bacterial, viral, parasite cultures, examination of stool

Secondary Evaluation (if enteric pathogens are not present)

1. Malabsorption studies
   Hydrogen breath test analysis
   Fecal fat determination
   Fecal elastase
   D-Xylose absorption
   Stool α1-antitrypsin
2. Radiographic studies (contrast, computed tomography, ultrasonography)

Tertiary Evaluation

1. Diagnostic endoscopy
   Biopsies, routine stains
   Brushings, cytology
   Duodenal aspirate (quantitative bacterial culture, ova and parasite)
   MAC culture, AFB stains (if HIV, CD4 count < 200 cells/mm^3)
   Electron microscopy
2. Motility studies (in the appropriate clinical setting)

AFB, acid-fast bacilli; MAC, *Mycobacterium avium-intracellulare* complex.

an absorbable sugar that does not require active transport for uptake by enterocytes. Thus, the D-xylose serum level, after administration of a test dose, reflects the absorptive ability of the gastrointestinal tract and the integrity of the mucosal surface. In younger children, the administered dose is 0.5 g per kg bodyweight, given orally after an overnight fast. In older children and adolescents, the maximum dose is 25 g. A serum level is obtained 1 hour after ingestion. Urine samples may be obtained for 5 hours after ingestion as well. Plasma citrulline levels correlate with enterocyte mass and function and may be used to indicate gastrointestinal function.[165]

Fat malabsorption is determined by a 72-hour fecal fat collection. A high-fat diet is administered several days before the collection is initiated and throughout the collection period. An alternative method is to keep a dietary fat intake record during the period of fecal fat collection. The stool is analyzed for total fat content, and the fecal fat is compared with the amount ingested; a coefficient of fat absorption is then calculated. Ten percent or more of ingested fat in the stool is considered abnormal. Alternatively, a Sudan stain may be performed on a random stool sample. This may be helpful as a quick test for fat malabsorption, although it is not so reliable. Quantification of fecal elastase may help to determine whether the fat malabsorption is pancreatic in origin. Lastly, raised fecal α_1-antitrypsin levels suggest protein loss from the gut.

If noninvasive studies, such as those described above, are not helpful in documenting and determining the etiology of the malabsorption, diarrhea, or vomiting, endoscopy (either upper or lower) with biopsy and appropriate culture of fluid may be useful. Miller et al.[41] confirmed histologic abnormalities in 72% of children undergoing upper endoscopy. In 70% of patients in this series, the clinical management of the child was changed because of the endoscopic evaluation. A high diagnostic yield has been supported by other investigators.[166] Specific gastrointestinal symptoms are not predictive of abnormal findings at endoscopy; advanced HIV-1 disease stage and an increased number of symptoms seem to be more predictive.[41] Histologic studies of the small bowel may aid in determining the degree of the villous blunting, and electron microscopy and special staining for opportunistic pathogens can be performed. Quantitative bacterial cultures and parasite evaluation of the duodenal fluid should be obtained when an endoscopy is performed. Characteristically, the detection of more than 10^5 organisms per milliliter of duodenal fluid confirms bacterial overgrowth. It is important to obtain both anaerobic and quantitative cultures. However, other studies have shown that endoscopy does not improve the diagnostic yield compared with stool examination in patients with intestinal infection. The only exception is the diagnosis of CMV.[167] An additional study found that flexible sigmoidoscopy was as useful as a full colonoscopy for diagnosing infection.[168] Special histologic stains for fungal, mycobacterial, or viral infections did not increase the diagnostic yield over routine hematoxylin and eosin staining.[169]

Treatment for intestinal infections has been outlined in Table 42-2 and previous sections. Therapy for gastrointestinal malabsorption should be directed toward the underlying diagnosis. If clinically symptomatic lactose malabsorption is found, a lactose-free diet should be initiated. Compliance may be difficult, because many foods contain lactose. Children can limit the effects of dietary lactose by taking exogenous lactase or using lactase-treated milk. There should be careful consideration of calcium and vitamin D intake, because children with HIV-1 infection are susceptible to low bone mineral density.[170-172] If there is malabsorption of protein and fat, a protein hydrolysate diet should be tried. Many of these supplements are poorly tolerated because they are unpalatable. In some circumstances, specialized supplements may need to be administered through a supplemental feeding tube.[173,174] Peptic and motility disorders can be treated as in other, non-HIV-1-infected children, paying careful attention to potential drug interactions with antiretroviral regimens.

OTHER SECONDARY IMMUNODEFICIENCIES

A variety of other disorders (Table 42-5) can cause secondary immunodeficiencies with effects on the gastrointestinal tract. Overall, these disorders are more prevalent than either primary or HIV-1-associated immunodeficiencies. Premature infants, children with cancer and associated exposure to immunosuppressant and cytotoxic medications (including children with graft-versus-host disease), and children with protein-losing enteropathy with associated loss of immunoglobulins from the gastrointestinal tract can all be immunodeficient because of the underlying disorder. In general, children with these immunodeficiencies are at risk for many of the same complications that are experienced by children with HIV-1 infection. Gastrointestinal tract infections are among the most common problems facing children with other secondary immunodeficiencies.

Malnutrition and Micronutrient Deficiencies

Malnutrition is the most common cause of immunodeficiency worldwide. Nutritional status and immunity have long been linked in many disease states. Before HIV-1 was described, *P. carinii* (now *jirovecii*) pneumonia and Kaposi's sarcoma,

TABLE 42-5. **Causes of Secondary Immunodeficiencies**

Prematurity
Metabolic disorders
Down syndrome
Malnutrition
Micronutrient deficiency
Uremia, nephrotic syndrome
Sickle cell disease
Diabetes mellitus
Protein-losing enteropathy
Immunosuppression
Drug
Radiation
Infectious diseases
HIV
Congenital rubella
Cytomegalovirus
Epstein-Barr virus
Acute bacterial disease
Disseminated fungal disease
Hematologic or malignancy
Leukemia, lymphoma, other malignancies
Graft-versus-host disease
Aplastic anemia, agranulocytosis
Surgery or trauma
Splenectomy
Burns
Inflammatory bowel disease
Systemic lupus erythematosus, other autoimmune diseases
Cirrhosis
Morbid obesity
Other chronic diseases of childhood

known opportunistic diseases, were first described in otherwise healthy, but malnourished, children and adults in developing nations.[175,176] This association led investigators to conclude that nutrition alone can affect the immunologic response of an individual. In malnourished children there is a profound involution of lymphoid tissues, including thymic atrophy and diminished paracortical regions of lymph nodes.[177] In young infants and children, protein-calorie malnutrition increases the risk of death by severalfold by increasing the susceptibility to infection.[178] In many countries, the mortality rate increases from 0.5% in children whose weight-for-height percentage of standard is greater than 80%, to 18% in children whose weight-for-height percentage of standard is less than 60%.[179] In other diseases such as cystic fibrosis and cancer, nutritional status has been linked closely to survival and morbidity. Malnourished children with leukemia and lymphoma have a higher risk of *P. jirovecii* pneumonia than children who have normal nutrition.[175]

Biochemically, protein-calorie malnutrition leads to changes in several aspects of the immune system. Cell-mediated immunity, microbial function of phagocytes, complement systems, secretory antibodies, and antibody affinity are consistently impaired in patients with significant malnutrition. Additionally, deficiencies of micronutrients, especially zinc and iron, as well as many others, may also have deleterious effects on the immune system. Other aspects of immunity that are altered by protein-calorie malnutrition include impaired chemotaxis of neutrophils, decreased lysozyme levels in serum and secretions, and interferon production in antibody response to T-cell-dependent antigens. A child with protein-calorie malnutrition may also have impaired mucosal immunity with lowered concentrations of secretory IgA in saliva, nasopharynx, tears, and the gastrointestinal tract compared with well-nourished control children.

Similar to children and adults with HIV-1 infection, patients with malnutrition have depressed T-cell function not only in the peripheral circulation but also in the intestinal tract. Subsequently, plasma cell function and macrophage activity may be impaired, leading to more frequent intestinal infections in children with severe protein-calorie malnutrition. Not only does nutrition improve the immunologic functioning of the intestinal tract, but nutrients themselves are trophic and essential for the maintenance of the absorptive capacity of the intestines. In some studies, weight loss greater than 30%, due to other disorders, is associated with a reduction in pancreatic enzyme secretion of over 80%, villous atrophy, and impaired carbohydrate and fat absorption.[180] These disorders are promptly reversed with appropriate nutritional rehabilitation. With villous blunting, antigen uptake can increase, leaving the child at higher risk of enteric infection. The pathogenesis of villous blunting is unclear but may be due to crypt hyperplasia as the primary event with premature sloughing at the villus tip[181] versus loss of enterocytes at the villus tip with resultant proliferation at the crypts.[182]

Malnutrition and its associated immunodeficiency are of global concern, and researchers have experimented with both dietary regimens and micronutrient supplementation to improve, and perhaps ultimately restore, adequate immunological function.[183,184] Because of the low cost of many micronutrients when compared to pharmacological agents, success in such experimentation could have profound implications for those suffering from malnutrition, as well as other immunocompromised patients.

Zinc is accepted as a promoter of immune function and consequently has been evaluated in HIV-1 immunocompromised patients. In a South African study that treated patients with 10 mg of zinc (elemental) daily for 6 months and compared them to a control group receiving a placebo, there was a significant difference in patient presentation of diarrhea favoring zinc supplementation.[185] Further demonstrating its potential alleviatory effects, Canani et al.[186] observed that the transactivating peptide's (Tat) secretory mechanism was inhibited by zinc and subsequently prevented diarrhea in pediatric HIV-1 patients. Both of these positive outcomes, although documented in HIV-1 patients, present zinc as an additional treatment option for symptoms of malnutrition-related immunodeficiency.

Some studies have administered multivitamins to HIV-1 patients including adults and children and evaluated effects of specific micronutrients. Adequate levels of vitamin A, when bolstered by supplementation in HIV-1 positive and HIV-1 negative children older than 6 months, correlated with reduced mortality and morbidity.[187] Although not yet well-documented in children, multivitamin intake of HIV-1 positive adults demonstrated retarded progression of the virus.[187] Improved hematologic status, mainly decreased rates of anemia, was observed in women and their children in Tanzania who were treated with iron supplements during and after pregnancy. This was marked by an average hemoglobin count that was 0.33 g/dL greater than that of the patient group who did not receive multivitamin treatment.[188] These findings underscore the need for additional randomized control trials in pediatric populations to further understand the role of micronutrient supplementation as a complimentary treatment component.

Immunosuppressive Therapy

Immunosuppressant medications are the mainstay of therapy for many diseases in children with autoimmune disorders, inflammatory bowel disease, chronic pulmonary disease, cancer, and organ transplantation. The best known immunosuppressants include corticosteroids, azathioprine, cyclosporin, tacrolimus, and anti-thymocyte globulin. Unfortunately, the effects of these medications are not targeted toward specific organs, but rather indiscriminately suppress immune function throughout the child. Thus, several immunologic functions including a decrease in monocyte adherence, neutrophil chemotaxis, and overall suppression of the inflammatory response are present. Children are at risk of enteric infections, similar to those described in children with HIV-1 infection. Pediatric patients undergoing transplant procedures, specifically solid organ transplant, are at increased risk of acquiring gastrointestinal infections when compared to their healthy counterparts. Acutely, these complications present with vomiting, diarrhea, and cramping. The most frequently diagnosed posttransplant infection is CMV,[189-191] but its onset has been reduced significantly with the administration of prophylactic drugs such as ganciclovir.[189-192]

LIVER COMPLICATIONS IN SECONDARY IMMUNODEFICIENCY

Another aspect of the gastrointestinal tract that renders importance in secondary immunodeficiency is the liver. Although data regarding liver complications in pediatric HIV-1 patients are lacking, there are considerable reports on HIV-1 infected

adults. Hepatitis coinfection, biliary tract disease, and drug-derived illness are some of the major complications we discuss in this section. Liver complications in secondary immunodeficiency, in their own right, deserve extensive coverage beyond the scope of this chapter, and so this section offers only a snapshot of this complex topic.

Hepatitis A, B, C Coinfection

Both hepatitis and HIV infections share similar transmission pathways, and for this reason, it is not surprising that rates of viral coinfections are considerable. Hepatitis A is often thought of as the less serious of the hepatitis viruses when treated promptly, and coinfection with HIV does not seem to predispose an individual to adverse outcomes. In 2006, coinfection rates of hepatitis B were reported to be between 5 and 10% in the global HIV population. Prolonged hepatitis B infection is one of the greatest concerns of for coinfected patients.[193] Hepatitis B virus e antigen (HBeAg) is the protein associated with active hepatitis B in patients and is used by clinicians to determine efficacy of medications. For monoinfected hepatitis B patients, proper treatment can result in significant reduction of HBeAg in 90 to 95% of patients; however, this success is not mirrored in HIV-coinfected populations.[194] There is also evidence for greater reactivation and replication in hepatitis B-HIV coinfected patients.[193,195-197] Explanation for this focuses on HIV patients' increased proinflammatory cytokine production and their inability to eliminate hepatocytes infected with hepatitis B.[196,198] Balancing dual treatment for both hepatitis B and HIV viruses presents a unique challenge for clinicians. Acquired mutations of hepatitis B render additional treatment considerations, deepening the challenge. Resistant hepatitis B strains have been identified, many of them falling under the tyrosine-methionine-aspartate-aspartate category, YMDD. Iacomi et al.[199] determined that 28 of 29 hepatitis B–HIV coinfected patients exhibited this specified resistance. Lamivudine, once commonly prescribed, has become less effective because of developed resistance. Of the various treatment options, only tenofovir is used in HIV treatment and is effective in both the wild-type hepatitis B virus and the resistant YMDD strain, and it is often concomitantly administered with emtricitabine.[200,201]

Mothers coinfected with hepatitis C and HIV are more likely to transmit HIV to their children, indicating greater risk of perinatal transmission in coinfected patients.[202,203] Liver disease in coinfected patients may be accelerated when compared to their monoinfected counterparts. Pathways that have been proposed to accelerate fibrosis in coinfected patients include direct viral effects, dysregulation of the immune system toward a profibrotic state, and other metabolic pathways that lead to liver toxicity and processes such as steatosis and insulin resistance.[204] Giovaninni et al.[203] studied 49 HIV-infected children, 11 of whom were coinfected with hepatitis C. Six of the coinfected patients had abnormal alanine aminotransferase (ALT) levels. Three of the six children had AIDS, and three had AIDS-related complex. Five children with normal aminotransferase had no detectable viral progression. Following acute hepatitis C infection, hepatitis C–HIV coinfected patients are over 20% more likely than monoinfected patients to develop chronic hepatitis C infection.[205-207] Interferon with ribavirin therapy is widespread in chronic hepatitis-C monoinfected patients, and its efficacy in hepatitis C–HIV coinfected patients is yet to be fully realized.[208,209] When compared to conventional interferon therapy (IFNα-2a), 180 μg/week pegylated interferon (pegIFNα-2a) plus 800 mg/day ribavirin demonstrated enhanced histological effects that were also associated with improved virological response in hepatitis C–HIV coinfected patients.[210] End-stage liver failure, cirrhosis, and hepatocellular carcinoma have been observed with greater frequency in hepatitis C–HIV coinfected patients.[205] These findings reflect adult populations and may or may not be indicative of outcomes in pediatric patients.

Biliary Tract Complications

Children with acute biliary tract disease may present with right-sided abdominal pain, vomiting, and jaundice. Also, elevated serum bile levels may induce pruritus. Despite a disproportionate increase in alkaline phosphatase levels, ALT levels may or may not be elevated. An ultrasound of the biliary system may be needed when serum sampling is equivocal. Biliary tract disease is often obstructive; thus, use of endoscopic retrograde cholangiopancreatography (ERCP) will help to identify the obstruction, perhaps provide bile sampling, and even mitigate the obstruction via sphincterotomy. Bile sampling may indicate the presence of CMV, *Cryptosporidium*, *Mycobacterium*, or microsporidia, which were all discussed in previous sections. In one study employing sonography, 26 of 41 HIV-infected children displayed hepatobiliary abnormalities, yet there was no evidence of infection.[211] AIDS cholangiopathy is defined by intra- and extrahepatic sclerosing cholangitis and is commonly linked to CMV and *Cryptosporidium* infections. Incidence in pediatric HIV populations remains to be thoroughly evaluated.

Treatment-Derived Complications

The advent of HAART, as discussed previously, has had profound effects on reducing many infections within the gastrointestinal tract. In the liver, however, there has been a negative association between receipt of antiretroviral therapy and development of liver complications, defined as *immune restoration hepatitis*.[193] Serum ALT elevation is associated with liver tissue damage and therefore is used to detect liver disease. Hepatitis-HIV patients on HAART present with elevated ALT levels in the blood principally derived from HAART-induced hepatotoxicity, resistance to antiretrovirals, and HAART noncompliancy.[212] Specifically, mitochondrial damage has been implicated as a contributor to liver death, which stems from coinfection and drug treatments.[213,214] Current research aims to determine effective methodology for detecting hepatic mitochondrial toxicity as a means to identify patients at risk of developing liver complications due to treatment.[213]

SUMMARY

Gastrointestinal disorders in children with secondary immunodeficiencies cause considerable comorbidity. Infection of the gastrointestinal tract is one the most common complications associated with secondary immunodeficiencies. However, malabsorption, peptic disease, and liver and biliary tract disease are also prevalent. These gastrointestinal complications contribute negatively to the overall clinical outcomes of children who have other chronic medical conditions, and they can often become life-threatening. Thus, clinicians should be vigilant and aggressive in the evaluation and treatment of gastrointestinal tract dysfunction in children with secondary immunodeficiencies.

REFERENCES

8. Gona P, Van Dyke RB, Williams PL, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. JAMA 2006;296:292–300.
35. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 2006;12:1365–1371.
62. Canani RB, Spagnuolo MI, Cirillo P, Guarino A. Ritonavir combination therapy restores intestinal function in children with advanced HIV disease. J Acquir Immune Defic Syndr 1999;21:307–312.
165. Crenn P, De Truchis P, Neveux N, et al. Plasma citrulline is a biomarker of enterocyte mass and an indicator of parenteral nutrition in HIV-infected patients. Am J Clin Nutr 2009;90:587–594.
178. Scrimshaw NS, Taylor CE, Gordon JE. Interactions of nutrition and infection. WHO Monograph Series World Health Organ 1968:57.
204. Kim AY, Chung RT. Coinfection with HIV-1 and HCV – a one-two punch. Gastroenterology 2009;137:795–814.

See expertconsult.com for a complete list of references and the review questions for this chapter.

REFERENCES

1. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. pediatric AIDS clinical trials group protocol 076 study group. N Engl J Med 1994;331:1173–1180.
2. CDC. HIV/AIDS Statistics and Surveillance. Available at <http://cdc.gov/hiv/topics/surveillance/factsheets.htm>.
3. Uauy R, Kain J, Mericq V, et al. Nutrition, child growth, and chronic disease prevention. Ann Med 2008;40:11–20.
4. Gallo RC, Salahuddin SZ, Popovic M, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 1984;224:500–503.
5. UNAIDS. AIDS epidemic update. Available at <http://www.unaids.org/en/resources/epidemiology.asp>; December 2008.
6. Kourtis AP, Duerr A. Prevention of perinatal HIV transmission: a review of novel strategies. Expert Opin Investig Drugs 2003;12:1535–1544.
7. van Rossum AM, Fraaij PL, de Groot R. Efficacy of highly active antiretroviral therapy in HIV-1 infected children. Lancet Infect Dis 2002;2:93–102.
8. Gona P, Van Dyke RB, Williams PL, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. JAMA 2006;296:292–300.
9. Brenchley JM, Schacker TW, Ruff LE, et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. J Exp Med 2004;200:749–759.
10. Mehandru S, Poles MA, Tenner-Racz K, et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. J Exp Med 2004;200:761–770.
11. Guadalupe M, Sankaran S, George MD. Viral suppression and immune restoration in the gastrointestinal mucosa of human immunodeficiency virus type 1-infected patients initiating therapy during primary or chronic infection. J Virol 2006;80:823.
12. Veazey RS, DeMaria M, Chalifoux LV, et al. Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection. Science 1998;280:427–431.
13. Daar ES, Moudgil T, Meyer RD, Ho DD. Transient high levels of viremia in patients with primary human immunodeficiency virus type 1 infection. N Engl J Med 1991;324:961–964.
14. Kinloch-De Loes S, Hirschel BJ, Hoen B, et al. A controlled trial of zidovudine in primary human immunodeficiency virus infection. N Engl J Med 1995;333:408–413.
15. Mellors JW, Rinaldo CRJ, Gupta P, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science 1996;272:1167–1170.
16. Wahl SM, Greenwell-Wild T, Peng G, et al. *Mycobacterium avium* complex augments macrophage HIV-1 production and increases CCR5 expression. Proc Natl Acad Sci USA 1998;95:12574–12579.
17. Smith PD, Saini SS, Raffeld M, et al. Cytomegalovirus induction of tumor necrosis factor-alpha by human monocytes and mucosal macrophages. J Clin Invest 1992;90:1642–1648.
18. McDonald D, Wu L, Bohks SM, et al. Recruitment of HIV and its receptors to dendritic cell-T cell junctions. Science 2003;300:1295–1298.
19. Frankel SS, Wenig BM, Burke AP, et al. Replication of HIV-1 in dendritic cell-derived syncytia at the mucosal surface of the adenoid. Science 1996;272:115–117.
20. Geijtenbeek TB, Kwon DS, Torensman R, et al. DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells. Cell 2000;100:587–597.
21. Cameron PU, Freudenthal PS, Barker JM, et al. Dendritic cells exposed to human immunodeficiency virus type-1 transmit a vigorous cytopathic infection to CD4+ T cells. Science 1992;257:383–387.
22. Fantini J, Cook DG, Nathanson N, et al. Infection of colonic epithelial cell lines by type 1 human immunodeficiency virus is associated with cell surface expression of galactosylceramide, a potential alternative gp 120 receptor. Proc Natl Acad Sci USA 1993;90:2700–2704.
23. Bomsel M. Transcytosis of infectious human immunodeficiency virus across a tight human epithelial cell line barrier. Nat Med 1997;3:42–47.
24. Meng G, Wei X, Wu X, et al. Primary intestinal epithelial cells selectively transfer R5 HIV-1 to CCR5+ cells. Nat Med 2002;8:150–156.
25. Meng G, Sellers M, Mosteller Barnum M, et al. Lamina propria lymphocytes, not macrophages, express CCR5 and CXCR4 and are likely target cell for HIV-1 in the intestinal mucosa. J Infect Dis 2000;182:785–791.
26. Smith PD, Meng G, Sellers MT, et al. Biological parameters of HIV-1 infection in primary intestinal lymphocytes and macrophages. J Leukoc Biol 2000;68:360–365.
27. Veazey RS, DeMaria M, Chalifoux LV, et al. Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection. Science 1998;280:427–431.
28. Burgio VT, Fais S, Boirivant M, et al. Peripheral monocyte and naive T-cell recruitment and activation in Crohn's disease. Gastroenterology 1995;109:1029–1038.
29. Poles MA, Boscardin WJ, Elliott J, et al. Lack of decay of HIV-1 in gut-associated lymphoid tissue reservoirs in maximally suppressed individuals. J Acquir Immune Defic Syndr 2006;43:65–68.
30. Kewenig S, Schneider T, Hohloch K, et al. Rapid mucosal $CD4^+$ T-cell depletion and enteropathy in simian immunodeficiency virus-infected rhesus macaques. Gastroenterology 1999;116:1115–1123.
31. Smythies LE, Sellers M, Clements RH, et al. Human intestinal macrophages display profound inflammatory anergy despite avid phagocytic and bacteriocidal activity. J Clin Invest 2005;115:66–75.
32. Wahl SM, Orenstein JM, Smith PD. Macrophage functions in HIV-1 infection. In: Gupta SD, editor. Immunology of Human Immunodeficiency Virus Type 1 Infection. New York: Plenum; 1996. p. 303–336.
33. Arthos J, Cicala C, Martinelli E, et al. HIV-1 envelope protein binds to and signals through integrin $\alpha4\beta7$, the gut mucosal homing receptor for peripheral T cells. Nat Immunol 2008;9:301–309.
34. Smith PD, Meng G, Salazar-Gonzalez JF, Shaw GM. Macrophage HIV-1 infection and the gastrointestinal tract reservoir. J Leukoc Biol 2003;74:642–649.
35. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 2006;12:1365–1371.
36. Douek DHIV. disease progression: immune activation, microbes, and a leaky gut. Top HIV Med 2007;15:114–117.
37. MacDonald T, Spencer J. Evidence that activated mucosal T cells play a role in the pathogenesis of enteropathy in human small intestine. J Exp Med 1988;167:1341–1349.
38. Kotler DP, Gaetz HP, Lange M, et al. Enteropathy associated with the acquired immunodeficiency syndrome. Ann Intern Med 1984;104:421–428.
39. Ullrich R, Zeitz M, Heise W, et al. Small intestinal structure and function in patients infected with human immunodeficiency virus (HIV): evidence for HIV-induced enteropathy. Ann Intern Med 1989;111:15–21.
40. Sankaran S, George MD, Reay E, et al. Rapid onset of intestinal epithelial barrier dysfunction in primary human immunodeficiency virus infection is driven by an imbalance between immune response and mucosal repair and regeneration. J Virol 2008;82:538–545.
41. Miller TL, McQuinn LB, Orav EJ. Endoscopy of the upper gastrointestinal tract as a diagnostic tool for children with human immunodeficiency infection. J Pediatr 1997;130:766–773.
42. Bjarnason I, Sharpstone DR, Frances DR, et al. Intestinal inflammation, ileal structure and function in HIV. AIDS 1996;10:1385–1391.
43. Carlson S, Yokoo H, Craig RM. Small intestinal human immunodeficiency virus-associated enteropathy: evidence for panintestinal enterocyte dysfunction. Lab Clin Med 1994;124:652–659.
44. Keating J, Bjarnason I, Somasundaram S, et al. Intestinal absorptive capacity, intestinal permeability and jejunal histology in human immunodeficiency virus and their relation to diarrhea. Gut 1995;37:623–629.
45. Lim SG, Menzies IS, Nukajam WS, et al. Intestinal disaccharidase activity in human immunodeficiency disease. Scand J Gastroenterol 1995;30:235–241.
46. Mosavi AJ, Hussain MF, DuPont HL, et al. Lack of correlation between diarrhea and weight loss in HIV-positive outpatients in Houston, TX. J Clin Gastroenterol 1995;21:61–64.
47. Taylor C, Hodgson K, Sharpstone D, et al. The prevalence and severity of intestinal disaccharidase deficiency in human immunodeficiency virus-infected subjects. Scand J Gastroenterol 2000;35:599–606.

48. Miller TL, Orav EJ, Martin SR, et al. Malnutrition and carbohydrate malabsorption in children with vertically-transmitted human immunodeficiency virus-1 infection. Gastroenterology 1991;100:1296–1302.
49. Italian Paediatric Intestinal/HIV Study Group. Intestinal malabsorption of HIV-infected children: relationship to diarrhoea, failure to thrive, enteric microorganisms and immune impairment. AIDS 1993;7:1435–1440.
50. Yolken RH, Hart W, Oung I, et al. Gastrointestinal-dysfunction and disaccharide intolerance in children infected with human immunodeficiency virus. J Pediatr 1991;118:359–363.
51. Sentongo TA, Rutstein RM, Stettler N, et al. Association between steatorrhea, growth, and immunologic status in children with perinatally acquired HIV infection. Arch Pediatr Adolesc Med 2001;155:149–153.
52. Carroccio A, Fontana M, Spagnuolo MI, et al. Pancreatic dysfunction and its association with fat malabsorption in HIV infected children. Gut 1998;43:558–563.
53. Schneider T, Jahn HV, Schmidt W, et al. Loss of CD4 T lymphocytes in patients infected with human immunodeficiency virus type 1 is more pronounced in the duodenal mucosa than in the peripheral blood. Gut 1995;37:524–529.
54. Canani RB, De Marco G, Passariello A, et al. Inhibitory effect of HIV-1 tat protein on the sodium-d-glucose symporter of human intestinal epithelial cells. AIDS 2006;20:5–10.
55. Kotler DP, Reka S, Clayton F. Intestinal mucosal inflammation associated with human immunodeficiency virus infection. Dig Dis Sci 1993;38:1119–1127.
56. Lake-Bakaar G, Tom W, Lake-Bakaar D, et al. Gastropathy and ketoconazole malabsorption in the acquired immunodeficiency syndrome (AIDS). Ann Intern Med 1988;109:471–473.
57. Smith PD, Lane HC, Gill VJ, et al. Intestinal infections in patients with the acquired immunodeficiency syndrome (AIDS): etiology and response to therapy. Ann Intern Med 1988;108:328–333.
58. Wilcox CM, Waites KB, Smith PD. No relationship between gastric pH, small bowel bacterial colonisation, and diarrhoea in HIV-1 infected patients. Gut 1999;44:101–105.
59. Ramos-Soriano AG, Saavedra JM, Wu TC, et al. Enteric pathogens associated with gastrointestinal dysfunction in children with HIV infection. Mol Cell Probes 1996;10:67–73.
60. Mönkemüller KE, Call SA, Lazenby AJ, Wilcox CM. Declining prevalence of opportunistic gastrointestinal disease in the era of combination antiretroviral therapy. Am J Gastroenterol 2000;95:457–462.
61. Epple HJ, Schneider T, Troeger H, et al. Impairment of the intestinal barrier is evident in untreated but absent in suppressively treated HIV-infected patients. Gut 2009;58:220–227.
62. Canani RB, Spagnuolo MI, Cirillo P, Guarino A. Ritonavir combination therapy restores intestinal function in children with advanced HIV disease. J Acquir Immune Defic Syndr 1999;21:307–312.
63. Poles MA, Fuerst M, McGowan I, et al. HIV-related diarrhea is multifactorial and fat malabsorption is commonly present, independent of HAART. Am J Gastroenterol 2001;96:1831–1837.
64. Monkemuller KE, Call SA, Lazenby AJ, Wilcox CM. Declining prevalence of opportunistic gastrointestinal disease in the era of combination antiretroviral therapy. Am J Gastroenterol 2000;95:457–462.
65. Brink AK, Mahe C, Watera C, et al. Diarrhea, CD4 counts and enteric infections in a community-based cohort of HIV-infected adults in Uganda. J Infect 2002;45:99–106.
66. Pui JC, Furth EE, Minda J, Montone KT. Demonstration of varicella-zoster virus infection in the muscularis propria and myenteric plexi of the colon in an HIV-positive patient with herpes zoster and small bowel pseudoobstruction (Ogilvie's syndrome). Am J Gastroenterol 2001;96:1627–1629.
67. Tendero DT. Laboratory diagnosis of cytomegalovirus (CMV) infections in immunodepressed patients, mainly in patients with AIDS. Clin Lab 2001;47:169–183.
68. Ukarapol N, Chartapisak W, Lertprasertsuk N, et al. Cytomegalovirus-associated manifestations involving the digestive tract in children with human immunodeficiency virus infection. J Pediatr Gastroenterol Nutr 2002;35:669–673.
69. Zanolla G, Resener T, Knebel R, Verney Y. Massive lower gastrointestinal hemorrhage caused by CMV disease as a presentation of HIV in an infant. Pediatr Surg Int 2001;17:65–67.
70. Pollok RC. Viruses causing diarrhoea in AIDS. Novartis Found Symp 2001;238:276–283.
71. Orenstein JM, Dieterich DT. The histopathology of 103 consecutive colonoscopy biopsies from 82 symptomatic patients with acquired immunodeficiency syndrome: original and look-back diagnoses. Arch Pathol Lab Med 2001;125:1042–1046.
72. Sabin CA, Clewley GS, Deayton JR, et al. Shorter survival in HIV-positive patients with diarrhoea who excrete adenovirus from the GI tract. J Med Virol 1999;58:280–285.
73. Grohmann GS, Glass RI, Monroe SS, et al. Enteric viruses and diarrhea in HIV-infected patients. N Engl J Med 1993;329:14–20.
74. Giordano MO, Martinez LC, Rinaldi D, et al. Detection of picobirnavirus in HIV-infected patients with diarrhea in Argentina. J Acquir Immune Defic Syndr Hum Retrovirol 1998;18; 380-380.
75. Cegielski JP, Msengi AE, Miller SE. Enteric viruses associated with HIV infection in Tanzanian children with chronic diarrhea. Pediatric AIDS HIV Infect 1994;5:296–299.
76. Belitsos PC, Greenson JK, Yardley JH, et al. Association of gastric hypoacidity with opportunistic enteric infections in 12 patients with AIDS. J Infect Dis 1992;166:277–284.
77. Gordon MA, Banda HT, Gondwe M, et al. Non-typhoidal *Salmonella* bacteraemia among HIV-infected Malawian adults: high mortality and frequent recrudescence. AIDS 2002;16:1633–1641.
78. Manfredi R, Calza L, Chiodo F. Enteric and disseminated *Campylobacter* species infection during HIV disease: a persisting but significantly modified association in the HAART era. Am J Gastroenterol 2002;97:510–511.
79. Orenstein JM, Kotler DP. Diarrheogenic bacterial enteritis in acquired immunodeficiency syndrome: a light and electron microscopy study of 52 cases. Hum Pathol 1995;26:481–492.
80. Kotler DP, Giang TT, Thim M, et al. Chronic bacterial enteropathy in patients with AIDS. J Infect Dis 1995;171:552–558.
81. Nightingale SD, Byrd LT, Southern PM, et al. Incidence of *Mycobacterim avium- intracellulare* complex bacteremia in human immunodeficiency virus-positive patients. J Infect Dis 1992;165:1082–1085.
82. Chaisson RE, Gallant JE, Keruly JC, Moore RD. Impact of opportunistic disease on survival in patients with HIV infection. AIDS 1998;12:29–33.
83. Rolla VC, Gadelha AJ, Accacio N, et al. Opportunistic diseases incidence and survival in AIDS patients who experienced very low CD4+ cell counts in the protease inhibitors era (TuPe 3341). Ninth International Conference on AIDS 2000; Durban, South Africa.
84. Gadelha A, Accacio N, Grinzstejn B, et al. Low incidence of colonization and no cases of disseminated *Mycobacterium avium* complex infection (DMAC) in Brazilian AIDS patients in the HAART era. Brazil J Infect Dis 2002;6:252–257.
85. Nguyen HN, Frank D, Handt S, et al. Severe gastrointestinal hemorrhage due to *Mycobacterium avium* complex in a patient receiving immunosuppressive therapy. Am J Gastroenterol 1999;94:232–235.
86. Race EM, Adelson Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. Lancet 1998;351:252–255.
87. Desimone JA, Babinchak TJ, Kaulback KR, Pomerantz RJ. Treatment of *Mycobacterium avium* complex immune reconstitution disease in HIV-1-infected individuals. AIDS Patient Care STDs 2003;17:617–622.
88. French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. HIV Med 2000;1:107–115.
89. Dunne M, Fessel J, Kumar P, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated *Mycobacterium avium* infection in patients with human immunodeficiency virus. Clin Infect Dis 2000;31:1245–1252.
90. Griffith DE. Risk-benefit assessment of therapies for *Mycobacterium avium* complex infections. Drug Saf 1999;21:137–152.
91. Hunter PR, Nichols G. Epidemiology and clinical features of *Cryptosporidium* infection in immunocompromised patients. Clin Microbiol Rev 2002;15:145–154.
92. Amadi B, Kelly P, Mwiya M, et al. Intestinal and systemic infection, HIV, and mortality in Zambian children with persistent diarrhea and malnutrition. J Pediatr Gastroenterol Nutr 2001;32:550–554.

93. Cegielski JP, Ortega YR, McKee S, et al. *Cryptosporidium, Enterocytozoon*, and *Cyclospora* infections in pediatric and adult patients with diarrhea in Tanzania. Clin Infect Dis 1999;28:314–321.
94. Nime FA, Burek JB, Page DL, et al. Acute enterocolitis in a human being infected with the protozoon *Cryptosporidium*. Gastroenterology 1976;70:592–598.
95. Mersel JL, Perera DR, Meligro C, Rubin CE. Overwhelming watery diarrhea associated with a cryptosporidium in an immunosuppressed patient. Gastroenterology 1976;70:1156–1160.
96. Botero JH, Castano A, Montoya MN, et al. A preliminary study of the prevalence of intestinal parasites in immunocompromised patients with and without gastrointestinal manifestations. Rev Inst Med Trop S Paulo 2003;45:197–200.
97. Westrope C, Acharya A. Diarrhea and gallbladder hydrops in an immunocompetent child with *Cryptosporidium* infection. Pediatr Infect Dis J 2001;20:1179–1181.
98. Calzetti C, Magnani G, Confalonieri D, et al. Pancreatitis caused by *Cryptosporidium parvum* in patients with severe immunodeficiency related to HIV infection. Ann Ital Med Int 1997;12:63–66.
99. MacKenzie WR, Hoxie NJ, Proctor ME, et al. A massive outbreak in Milwaukee of *Cryptosporidium* infection transmitted through the public water supply. N Engl J Med 1994;331:161–167.
100. Kazlow PG, Shah K, Benkov KJ, et al. Esophageal cryptosporidiosis in a child with acquired immune deficiency syndrome. Gastroenterology 1986;91:1301–1303.
101. Clayton F, Heller T, Kotler DP. Variation in the enteric distribution of cryptosporidia in acquired immunodeficiency syndrome. Am J Clin Pathol 1994;102:420–425.
102. Goodgame RW, Kimball K, Ou CN, et al. Intestinal function and injury in acquired immunodeficiency-related cryptosporidiosis. Gastroenterology 1995;108:1075–1082.
103. Pettoello-Mantovani M, Di Martino L, Dettori G, et al. Asymptomatic carriage of intestinal *Cryptosporidium* in immunocompetent and immunodeficient children: a prospective study. Pediatr Infect Dis J 1995;14:1042–1047.
104. Soave R, Johnson WD. *Cryptosporidium* and *Isospora belli* infection. J Infect Dis 1988;157:225–229.
105. Kreinik G, Burstein O, Landor M, et al. Successful management of intractable cryptosporidial disease with intravenous octreotide, a somatostatin analogue. AIDS 1991;5:765–767.
106. Miao YM, Awad El Kariem FM, Franzen C, et al. Eradication of cryptosporidia and microsporidia following successful antiretroviral therapy. J Acquir Immune Defic Syndr 2000;25:124–129.
107. Schmidt W, Wahnschaffe U, Schafer M, et al. Rapid increase of mucosal CD4 T cells followed by clearance of intestinal cryptosporidiosis in an AIDS patient receiving highly active antiretroviral therapy. Gastroenterology 2001;120:984–987.
108. Simon D, Weiss L, Tanowitz HB, Wittner M. Resolution of *Cryptosporidium* infection in an AIDS patient after improvement of nutritional and immune status with octreotide. Am J Gastroenterol 1991;86:615–618.
109. Nord J, Pearl M, DiJohn D, et al. Treatment with hyperimmune colostrum of cryptosporidial diarrhea in AIDS patients. AIDS 1990;4:581–584.
110. Ungar BL, Ward DJ, Fayer R, Quinn CA. Cessation of *Cryptosporidium*-associated diarrhea in an acquired immunodeficiency patient after treatment with hyperimmune bovine colostrum. Gastroenterology 1990;98:486–489.
111. Hicks P, Zwiener J, Squires J, Savell V. Azithromycin therapy for *Cryptosporidium parvum* infection in 4 children infected with HIV. J Pediatr 1996;129:297–300.
112. Kadappu KK, Nagaraja MV, Rao PV, Shastry BA. Azithromycin as treatment for cryptosporidiosis in human immunodeficiency virus disease. J Postgrad Med 2002;48:179–181.
113. Hommer V, Eichholz J, Pertry F. Effect of antiretroviral protease inhibitors alone, and in combination with paromomycin, on the excystation, invasion and in vitro development of *Cryptosporidium parvum*. J Antimicrob Chemother 2003;52:359–364.
114. Abubakar I, Aliyu SH, Arumugam C, et al. Prevention and treatment of cryptosporidiosis in immunocompromised patients. Cochrane Database Syst Rev 2007;1(1):CD004932.
115. Bryan RT, Cali A, Owen RL, Spencer HC. Microsporidia: opportunistic pathogens in patients with AIDS. Prog Clin Parasitol 1991;2:1–26.
116. Desportes I, Le Charpentier Y, Galian A, et al. Occurrence of a new microsporidian: *Enterocytozoon bieneusi* n.g., n. sp., in the enterocytes of a human patient with AIDS. J Protozool 1985;32:250–254.
117. Orenstein JM, Chiang J, Steinberg W, et al. Intestinal microsporidiosis as a cause of diarrhea in human immunodeficiency virus infected patients: a report of 20 cases. Hum Pathol 1990;21:475–481.
118. Molina JM, Sarfati C, Beauvais B, et al. Intestinal microsporidiosis in human immunodeficiency virus-infected patients with chronic unexplained diarrhea: prevalence and clinical and biologic features. J Infect Dis 1993;167:217–221.
119. Coyle CM, Wittner M, Kotler DP, et al. Prevalence of microsporidiosis due to *Enterocytozoon bieneusi* and *Enterocytozoon* (*Septata*) *intestinalis* among patients with AIDS-related diarrhea: determination of polymerase chain reaction to the microsporidian small-subunit rRNA gene. Clin Infect Dis 1996;23:1002–1006.
120. Kotler DP, Orenstein JM. Prevalence of intestinal microsporidia in HIV-infected individual referred for gastroenterological evaluation. Am J Gastroenterol 1994;89:1998–2002.
121. Wanachiwanawin D, Chokephaibulkit K, Lertlaituan P, et al. Intestinal microsporidiosis in HIV-infected children with diarrhea. SE Asian J Trop Med Public Health 2002;33:241–245.
122. Tumwine JK, Kekitiinwa A, Nabukeera N, et al. *Enterocytozoon bieneusi* among children with diarrhea attending Mulago Hospital in Uganda. Am J Trop Med Hyg 2002;67:299–303.
123. Orenstein JM. Diagnostic pathology of microsporidiosis. Ultrastruct Pathol 2003;27:141–149.
124. Molina JM, Goguel J, Sarfati C, et al. Potential efficiency of funagillin in intestinal microsporidiosis due to *Enterocytozoon bieneusi* in patients with HIV infection: results of a drug screening study. AIDS 1997;11:1603–1610.
125. Coyle CM, Kent M, Tanowitz HB, et al. NP 470 is an effective antimicrosporidial agent. J Infect Dis 1998;177:515–518.
126. Didier ES. Effects of albendazole, fumagillin and TNP-470 on microsporidial replication in vitro. Antimicrob Agents Chemother 1997;41:1541–1546.
127. Anwar-Bruni DM, Hogan SE, Schwartz DA, et al. Atovaquone is effective treatment for the symptoms of gastrointestinal microsporidiosis in human immunodeficiency virus-1 infected patients. AIDS 1996;10:619–623.
128. Conteas CN, Berlin OGW, Ash LR, Pruthi JS. Therapy for human gastrointestinal microsporidiosis. Am J Trop Med Hyg 2000;63:121–127.
129. Maggi P, Larocca AM, Quarto M, et al. Effect of antiretroviral therapy on cryptosporidiosis and microsporidiosis in patients infected with human immunodeficiency virus type 1. Eur J Clin Microbiol Infect Dis 2000;19:213–217.
130. Verdier RI, Fitzgerald DW, Johnson WD, Pape JW. Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of *Isospora belli* and *Cyclospora cayetanensis* infection in HIV-infected patients. A randomized, controlled trial. Ann Intern Med 2000;132:885–888.
131. Weiss LM, Perlman DC, Sherman J, et al. *Isospora belli* infection: treatment with pyrimethamine. Ann Intern Med 1988;109:474–475.
132. Germani Y, Minssart P, Vohito M, et al. Etiologies of acute, persistent, and dysenteric diarrheas in adults in Bangui, Central African Republic, in relation to human immunodeficiency virus serostatus. Am J Trop Med Hyg 1998;59:1008–1014.
133. Chiou CC, Groll AH, Gonzalez CE, et al. Esophageal candidiasis in pediatric acquired immunodeficiency syndrome: clinical manifestations and risk factors. Pediatr Infect Dis 2000;19:729–734.
134. Saag MS, Fessel WJ, Kaufman CA, et al. Treatment of fluconazole-refractory oropharyngeal candidiasis with itraconazole oral solution in HIV-positive patients. AIDS Res Hum Retroviruses 1999;15:1413–1417.
135. Groll AH, Wood L, Roden M, et al. Safety, pharmacokinetics, and pharmacodynamics of cyclodextrin itraconazole in pediatric patients with oropharyngeal candidiasis. Antimicrob Agents Chemother 2002;46:2554–2563.
136. Suh KN, Anekthananon T, Mariuz PR. Gastrointestinal histoplasmosis in patients with AIDS: case report and review. Clin Infect Dis 2001;32:483–491.

137. Wheat LJ, Connolly Stringfield PA, Baker RL, et al. Disseminated histoplasmosis in the acquired immune deficiency syndrome: clinical findings, diagnosis and treatment, and review of the literature. Medicine 1990;69:361–374.
138. Suksomboon N, Poolsup N, Ket-Aim S. Systematic review of the efficacy of antiretroviral therapies for reducing the risk of mother-to-child transmission of HIV infection. J Clin Pharmacol Ther 2007;32:293–311.
139. Volmink J, Siegfried NL, van der Merwe L, Brocklehurst P. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev 2007; (1):CD003510.
140. Ylitalo N, Brogly S, Hughes MD, et al. Pediatric AIDS Clinical Trials Group Protocol 219C Team. Risk factors for opportunistic illnesses in children with human immunodeficiency virus in the era of highly active antiretroviral therapy. Arch Pediatr Adolesc Med 2006;160:778–787.
141. Nesheim SR, Kapogiannis BG, Soe MM, et al. Trends in opportunistic infections in the pre- and post-highly active antiretroviral therapy eras among HIV-infected children in the perinatal AIDS collaborative transmission study, 1986-2004. Pediatrics 2007;120:100–109.
142. Nachman S, Gona P, Dankner W, et al. The rate of serious bacterial infections among HIV-infected children with immune reconstitution who have discontinued opportunistic infection prophylaxis. Pediatrics 2005;115:e488–e494.
143. Buchner AM, Sonnenberg A. Medical diagnoses and procedures associated with *Clostridium difficile* colitis. Am J Gastroenterol 2001;96:766–772.
144. Pulvirenti JJ, Mehra T, Hafiz I, et al. Epidemiology and outcome of *Clostridium difficile* infection and diarrhea in HIV infected inpatients. Diag Microbiol Infect Dis 2002;44:325–330.
145. Anastasi JK, Capili B. HIV and diarrhea in the era of HAART: 1998 New York State hospitalizations. Am J Infect Control 2000;28:262–266.
146. Sanchez TH, Brooks JT, Sullivan PS, et al. Adult/Adolescent Spectrum of HIV Disease Study Group. Bacterial diarrhea in persons with HIV infection, United States, 1992-2002. Clin Infect Dis 2005;41:1621–1627.
147. AliMohamed F, Lule GN, Nyong'o A, et al. Prevalence of *Helicobacter pylori* and endoscopic findings in HIV seropositive patients with upper gastrointestinal tract symptoms at Kenyatta National Hospital, Nairobi. East Afr Med J 2002;79:226–231.
148. Sud A, Ray P, Bhasin DK, et al. *Helicobacter pylori* in Indian HIV infected patients. Trop Gastroenterol 2002;23:79–81.
149. Fernando N, Holton J, Zulu I, et al. *Helicobacter pylori* infection in an urban African population. J Clin Microbiol 2001;39:1323–1327.
150. Lichterfeld M, Lorenz C, Nischalke HD, et al. Decreased prevalence of *Helicobacter pylori* infection in HIV patients with AIDS defining diseases. Z Gastroenterol 2002;40:11–14.
151. Ribeiro JM, Lucas M, Palhano MJ, Victorino RM. Remission of a high-grade gastric mucosa associated lymphoid tissue (MALT) lymphoma following *Helicobacter pylori* eradication and highly active antiretroviral therapy in a patient with AIDS. Am J Med 2001;111:328–329.
152. Werneck-Silva AL, Prado IB. Dyspepsia in HIV-infected patients under highly active antiretroviral therapy. J Gastroenterol Hepatol 2007;22:1712–1716.
153. Griffin GE, Miller A, Batman P, et al. Damage to jejunal intrinsic autonomic nerves in HIV infection. AIDS 1988;2:379–382.
154. Neild PJ, Evans DF, Castilla FD, et al. Effect of octreotide on small intestinal motility in HIV-infected patients with chronic refractory diarrhea. Dig Dis Sci 2001;46:2636–2642.
155. Neild P, Nijran KS, Yazaki E, et al. Delayed gastric emptying in hu man immunodeficiency virus infection: correlation with symptoms, autonomic function, and intestinal motility. Dig Dis Sci 2000;45:1491–1499.
156. Zalar AE, Olmos MA, Piskorz EL, Magnanini FL. Esophageal motility disorders in HIV patients. Dig Dis Sci 2003;48:962–967.
157. Konturek JW, Fischer H, van der Voort IR, Domschke W. Disturbed gastric motor activity in patients with human immunodeficiency virus infection. Scand J Gastroenterol 1997;32:221–225.
158. Blitman NM, Ali M. Idiopathic giant esophageal ulcer in an HIV-positive child. Pediatr Radiol 2002;32:907–909.
159. Kotler DP, Reka S, Orenstein JM, Fox CH. Chronic idiopathic esophageal ulceration in the acquired immunodeficiency syndrome, characterization and treatment with corticosteroids. J Clin Gastroenterol 1992;15: 284–290.
160. Wilcox CM, Schwartz DA, Clark WS. Esophageal ulceration in human immunodeficency virus infection. Ann Intern Med 1995;122: 143–149.
161. Naum SM, Molloy PJ, Kania RJ, et al. Use of thalidomide in treatment and maintenance of idiopathic esophageal ulcers in HIV+ individuals. Dig Dis Sci 1995;40:1147–1148.
162. Jacobson JM, Spritzler J, Fox L, et al. Thalidomide for the treatment of esophageal aphthous ulcers in patients with human immunodeficiency virus infection. National Institute of Allergy and Infectious Disease AIDS Clinical Trials Group. J Infect Dis 1999;180:61–67.
163. Jacobson JM, Greenspan JS, Spritzler J, et al. Thalidomide in low intermittent doses does not prevent recurrence of human immunodeficiency virus-associated aphthous ulcers. J Infect Dis 2001;183:343–346.
164. Bini EJ, Micale PL, Weinshel EH. Natural history of HIV-associated esophageal disease in the era of protease inhibitor therapy. Dig Dis Sci 2000;45:1301–1307.
165. Crenn P, De Truchis P, Neveux N, et al. Plasma citrulline is a biomarker of enterocyte mass and an indicator of parenteral nutrition in HIV-infected patients. Am J Clin Nutr 2009;90:587–594.
166. Bashir RM, Wilcox CM. Symptom-specific use of upper gastrointestinal endoscopy in human immunodeficiency virus-infected patients yields high dividends. J Clin Gastroenterol 1996;23:292–298.
167. Weber R, Ledergerber B, Zbinden R, et al. Enteric infections and diarrhea in human immunodeficiency virus-infected persons: prospective community-based cohort study. Swiss HIV cohort study. Arch Intern Med 1999;159:1473–1480.
168. Kearney DJ, Steuerwald MS, Koch J, Cello JP. A prospective study of endoscopy in HIV-associated diarrhea. Am J Gastroenterol 1999;94: 596–602.
169. Monkemuller KE, Bussian AH, Lazenby AJ, Wilcox CM. Special histologic stains are rarely beneficial for the evaluation of HIV-related gastrointestinal infections. Am J Clin Pathol 2000;114:387–394.
170. Jacobson D, Spiegelman D, Duggan C, et al. Predictors of bone mineral density in human immunodeficiency virus-1 infected children. J Pediatr Gastroenterol Nutr 2005;41:339–346.
171. Purdy JB, Gafni RI, Reynolds JC, et al. Decreased bone mineral density with off-label use of tenofovir in children and adolescents infected with human immunodeficiency virus. J Pediatr 2008;152:582–584.
172. Mora S, Zamproni I, Cafarelli L, et al. Alterations in circulating osteoimmune factors may be responsible for high bone resorption rate in HIV-infected children and adolescents. AIDS 2007;21:1129–1135.
173. Miller TL, Awnetwant EL, Evans S, et al. Gastrostomy tube supplementation for HIV-infected children. Pediatrics 1995;96:696–702.
174. Henderson RA, Saavedra JM, Perman JA, et al. Effect of enteral tube feeding on growth of children with symptomatic human immunodeficiency virus infection. J Pediatr Gastroenterol Nutr 1994;18:429–434.
175. Chandra RK, editor. Immunocompetence of Nutritional Disorders. London: Arnold; 1980.
176. Centers for Disease Control. Task Force on Kaposi's Sarcoma and Opportunistic Infections. Epidemiologic aspects of the current outbreak of Kaposi's sarcoma and opportunistic infection. N Engl J Med 1982;306:248–252.
177. Chandra RK, Newberne PM, editors. Nutrition, Immunity and Infection: Mechanisms of Interactions. New York: Plenum; 1977.
178. Scrimshaw NS, Taylor CE, Gordon JE. Interactions of nutrition and infection. WHO Monograph Series World Health Organ 1968:57.
179. Hughes WT, Price RA, Sisko F, et al. Protein-calorie malnutrition: a host determinant for *Pneumocystis carinii* infection. Am J Dis Child 1974;128:44–52.
180. O'Keefe SJ. Nutrition and gastrointestinal disease. Scand J Gastroenterol 1996;220S:52–59.
181. Bhan MK. The gut in malnutrition. In: Walker WA, editor. Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, and Management. 3rd ed Philadelphia: BC Decker; 1991. p. 603–612.
182. Booth CC. The enterocyte in celiac disease. Brit Med J 1970;3:725–731.
183. Hendricks MK, Eley B, Bourne LT. Nutrition and HIV/AIDS in infants and children in South Africa: implications for food-based dietary guidelines. Matern Child Nutr 2007;3:322–333.

184. Irlam JH, Visser ME, Rollins N, Siegfried N. Micronutrient supplementation in children and adults with HIV infection. Cochrane Database Syst Rev 2005(4):CD003650.
185. Bobat R, Coovadia H, Stephen C, et al. Safety and efficacy of zinc supplementation for children with HIV-1 infection in South Africa: a randomised double-blind placebo-controlled trial. Lancet 2005;366:1862–1867.
186. Canani RB, Ruotolo S, Buccigrossi V, et al. Zinc fights diarrhoea in HIV-1-infected children: in-vitro evidence to link clinical data and pathophysiological mechanism. AIDS 2007;21:108–110.
187. Fawzi W, Msamanga G, Spiegelman D, Hunter DJ. Studies of vitamins and minerals and HIV transmission and disease progression. J Nutr 2005;135:938–944.
188. Fawzi WW, Msamanga GI, Kupka R, et al. Multivitamin supplementation improves hematologic status in HIV-infected women and their children in Tanzania. Am J Clin Nutr 2007;85:1335–1343.
189. Torres-Madriz G, Boucher HW. Immunocompromised hosts: perspectives in the treatment and prophylaxis of cytomegalovirus disease in solid-organ transplant recipients. Clin Infect Dis 2008;47:702–711.
190. Bueno J, Ramil C, Green M. Current management strategies for the prevention and treatment of cytomegalovirus infection in pediatric transplant recipients. Paediatr Drugs 2002;4:279–290.
191. McGavin JK, Goa KL. Ganciclovir: an update of its use in the prevention of cytomegalovirus infection and disease in transplant recipients. Drugs 2001;61:1153–1183.
192. Spivey JF, Singleton D, Sweet S, et al. Safety and efficacy of prolonged cytomegalovirus prophylaxis with intravenous ganciclovir in pediatric and young adult lung transplant recipients. Pediatr Transplant 2007;11:312–318.
193. Benhamou Y. Hepatitis B in the HIV-coinfected patient. J Acquir Immune Defic Syndr 2007;45(Suppl. 2):S57.
194. Thimme R, Spangenberg HC, Blum HE. Hepatitis B or hepatitis C and human immunodeficiency virus infection. J Hepatol 2005;42(Suppl. 1): S37–S44.
195. Di Martino V, Thevenot T, Colin JF, et al. Influence of HIV infection on the response to interferon therapy and the long-term outcome of chronic hepatitis B. Gastroenterology 2002;123:1812–1822.
196. Koblin BA, Taylor PE, Rubinstein P, Stevens CE. Effect of duration of hepatitis B virus infection on the association between human immunodeficiency virus type-1 and hepatitis B viral replication. Hepatology 1992;15:590–592.
197. Rustgi VK, Hoofnagle JH, Gerin JL, et al. Hepatitis B virus infection in the acquired immunodeficiency syndrome. Ann Intern Med 1984;101: 795–797.
198. Miller TL, Jonas MM. Adolescent human immunodeficiency virus infection and gastrointestinal disease. In: Belfus LC, editor. Adolescent Medicine: State of the Art Reviews. Philadelphia: Hanley and Belfus; 1995.
199. Iacomi F, Vincenti D, Vairo F, et al. Effect of HIV co-infection on mutation patterns of HBV in patients with lamivudine-resistant chronic hepatitis. Brit J Med Virol 2009;81:1151–1156.
200. Soriano V, Tuma P, Vispo E, et al. Hepatitis B in HIV patients: What is the current treatment and what are the challenges? J HIV Ther 2009;14: 13–18.
201. Peters MG. Diagnosis and management of hepatitis B virus and HIV coinfection. Top HIV Med 2007;15:163–166.
202. Bonacini M, Puoti M. Hepatitis C in patients with human immunodeficiency virus infection: diagnosis, natural history, meta-analysis of sexual and vertical transmission, and therapeutic issues. Arch Intern Med 2000;160:3365–3373.
203. Giovannini M, Tagger A, Ribero ML, et al. Maternal-infant transmission of hepatitis C virus and HIV infections: A possible interaction. Lancet 1990;335:1166.
204. Kim AY, Chung RT. Coinfection with HIV-1 and HCV – a one-two punch. Gastroenterology 2009;137:795–814.
205. Matthews GV, Dore GJ. HIV and hepatitis C coinfection. J Gastroenterol Hepatol 2008;23:1000–1008.
206. Mehta SH, Cox A, Hoover DR, et al. Protection against persistence of hepatitis C. Lancet 2002;359:1478–1483.
207. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA 2000;284:450–456.
208. Martin P, Jensen DM. Ribavirin in the treatment of chronic hepatitis C. J Gastroenterol Hepatol 2008;23:844–855.
209. Plosker GL, Keating GM. Peginterferon-α-2a (40kD) plus ribavirin: a review of its use in hepatitis C virus and HIV co-infection. Drugs 2004;64:2823–2843.
210. Lissen E, Clumeck N, Sola R, et al. Histological response to pegIFNα-2a (40KD) plus ribavirin in HIV-hepatitis C virus co-infection. AIDS 2006;20:2175–2181.
211. Chung CJ, Sivit CJ, Rakusan TA, et al. Hepatobiliary abnormalities on sonography in children with HIV infection. J Ultrasound Med 1994;13:205–210.
212. BHIVA Guidelines: HIV and chronic hepatitis: co-infection with HIV and hepatitis B virus infection [Internet]; c2005 [cited 2007 March 6]. Available at <http://www.bhiva.org/guidelines/2005/BHIVA-guidelines/index.html>.
213. Banasch M, Knyhala K, Kollar S, et al. Disease- and treatment-related predictors of hepatic mitochondrial dysfunction in chronic HIV infection assessed by non-invasive ^{13}C-methionine breath test diagnostic. Eur J Med Res 2008;13:401–408.
214. Van Huyen JP, Batisse D, Heudes D, et al. Alteration of cytochrome oxidase subunit I labeling is associated with severe mitochondropathy in NRTI-related hepatotoxicity in HIV patients. Mod Pathol 2006;19: 1277–1288.