Gastrointestinal manifestations of HIV infection

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As patients with human immunodeficiency virus (HIV) infection become more immunocompromised, gastrointestinal symptoms become more common. Most symptoms result from opportunistic infections and can be diagnosed and treated by gastroenterologists, although medical microbiology and histopathology input is essential.

Since the advent of combination antiretroviral therapy many patients with human immunodeficiency virus (HIV) infection have been able to enjoy prolonged periods of symptom-free good health (Palella et al, 1998). Eventually, however, breakthrough viraemia occurs because of viral resistance or poor compliance with drug regimens which may entail 30 or more tablets per day. Furthermore, for the majority of HIV-infected patients in the world, triple or quadruple antiretroviral therapy is an unaffordable dream. For these reasons gastrointestinal manifestations of HIV infection will be encountered by many gastroenterologists for the foreseeable future.

OESOPHAGEAL DISEASE

Dysphagia and odynophagia are common symptoms, and may be the presenting feature of acquired immunodeficiency syndrome (AIDS). *Candida* is the most frequent cause, and if oropharyngeal candidiasis is present a presumptive diagnosis of oesophageal *Candida* can be made without further investigation. Treatment with antifungals is usually rapidly effective (Dieterich and Wilcox, 1996). However, if symptoms persist after treatment, dysphagia is particularly severe or there is no oral *Candida* then upper gastrointestinal endoscopy is indicated.

Herpes simplex virus causes exquisitely painful oesophageal ulceration, usually with such severe dysphagia that the patient is unable to eat. It is rare nowadays, because many HIV-positive patients take regular acyclovir for prophylaxis against recurrent genital herpes. Endoscopy shows multiple small (2–5 mm) shallow ulcers, and occasionally vesicles. Treatment with acyclovir is effective but the drug may need to be given intravenously because of the severity of the dysphagia.

Cytomegalovirus (CMV) also causes oesophageal ulceration, but in this case the ulcers are larger, may be linear or serpiginous and are often rather deep. A diffuse oesophagitis can also occur. The diagnosis can be confirmed histologically, but it is essential to take biopsies from the granulation tissue in the base of the ulcer, as inclusions are rarely seen in biopsies taken from the squamous epithelium at the edge.

Sometimes large round or oval oesophageal ulcers are seen with no evidence of infection on biopsy or culture. These are 'giant aphthous ulcers' and can occur anywhere in the oesophagus and at any stage of HIV infection. A variety of treatments have been suggested including oral thalidomide and intralesional methylprednisolone (Dieterich and Wilcox, 1996).

Other conditions occasionally affecting the oesophagus include *Mycobacterium avium intracellulare* (MAI), lymphoma and Kaposi's sarcoma. The latter is almost always asymptomatic and rarely requires specific treatment.

DIARRHOEA

Diarrhoea is common at all stages of HIV infection, but in patients with relatively preserved immune function is usually transient, self-limited and not associated with chronic intestinal infection (Blanshard and Gazzard, 1993). In contrast, patients with CD4 counts less than 200/μl frequently have chronic debilitating diarrhoea. In more than 80% of these patients an identifiable gut infection is responsible, and up to 30% have multiple pathogens. Diarrhoea is

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particularly common in homosexual men, and may be caused by oral–anal transmission of enteric pathogens.

Non-opportunistic pathogens

Giardia, *Salmonella*, *Shigella* and *Campylobacter* can occur at any stage of HIV infection. Giardiasis may be difficult to diagnose, requiring multiple stool examinations and occasionally duodenal biopsy or aspiration, but readily responds to treatment with metronidazole or tinidazole. The pathogenic enteric bacteria are more commonly associated with septicaemia in AIDS patients than the general population, and for this reason antimicrobial treatment is recommended. Relapse is common where the CD4 count is less than 200/µl, so maintenance treatment may be necessary. *Campylobacter* species other than *C. jejuni* may occasionally be responsible for AIDS-related diarrhoea, and require special culture media to detect (Snijders et al, 1997).

Opportunistic pathogens

Microsporidia: Microsporidia are tiny intracellular protozoan parasites which do not usually infect immunocompetent individuals. A number of species cause gastrointestinal and disseminated infection in AIDS patients, usually once the CD4 count is less than 100/µl. Although the human infection was unknown before 1984, microsporidiosis is now identified commonly as cryptosporidiosis (*Figure 1*). The source of the infection is unknown and seasonal variations in incidence do not occur.

The most common species, *Enterocytozoon bieneusi*, infects the enterocytes of the small intestine but does not disseminate. *Encephalitozoon intestinalis* also causes diarrhoea, but disseminates from the intestine and multiorgan infection occurs. Intestinal microsporidiosis is diagnosed by identification of the spores in stools: fluorescent (van Gool et al, 1993) or trichrome stains (Weber et al, 1992) are the most sensitive. Distal duodenal biopsies are also useful (*Figure 2*).

Experienced histopathologists are usually able to identify the organism by light microscopy, particularly if special stains are used (Peacock et al, 1991), but occasionally electron microscopy (EM) may be required for confirmation. The two intestinal species may be distinguished by the size of their spores in the stool, their EM appearances or by polymerase chain reaction. This is important because species other than *E. bieneusi* are usually eradicated by albendazole treatment; *E. bieneusi* is not, but the diarrhoea may be improved (Blanshard et al, 1992a). More recently, thalidomide (Sharpstone et al, 1997) and atavaquone (Anwar-Bruni et al, 1996) have been proposed as treatments for *E. bieneusi* infection. Controlled trials are awaited with interest.

Cryptosporidia: Cryptosporidial infection shows a seasonal variation in incidence and usually causes fairly profuse watery diarrhoea (Blanshard et al, 1992b). The organism has long been thought to be a zoonosis, with infection from cattle being transmitted to humans via contaminated drinking water. Certainly a number of documented water-borne outbreaks

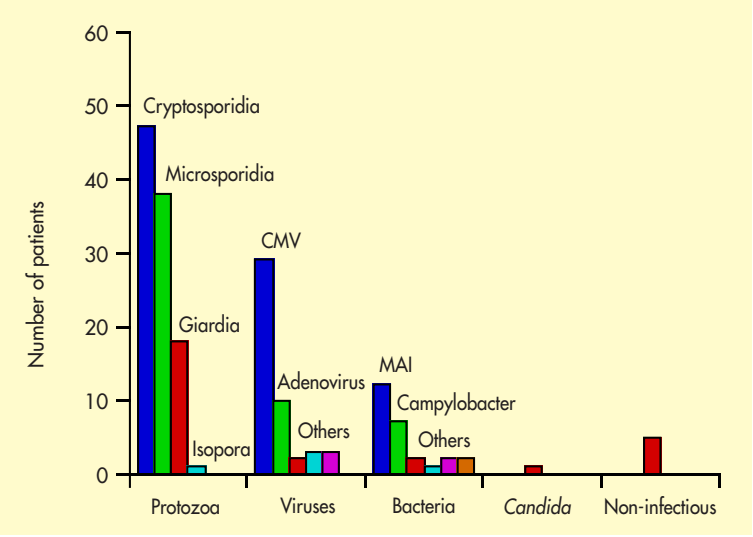

***Figure 1. Causes of chronic diarrhoea in 150 patients with acquired immunodeficiency syndrome. The non-infectious causes include lymphoma, extensive small bowel Kaposi's sarcoma, radiation proctitis and inflammatory bowel disease. Doubtful pathogens such as* Blastocystis hominis*, spirochaetes and non-invasive* Entamoeba histolytica *are excluded. CMV = cytomegalovirus; MAI =* Mycobacterium avium intracellulare.

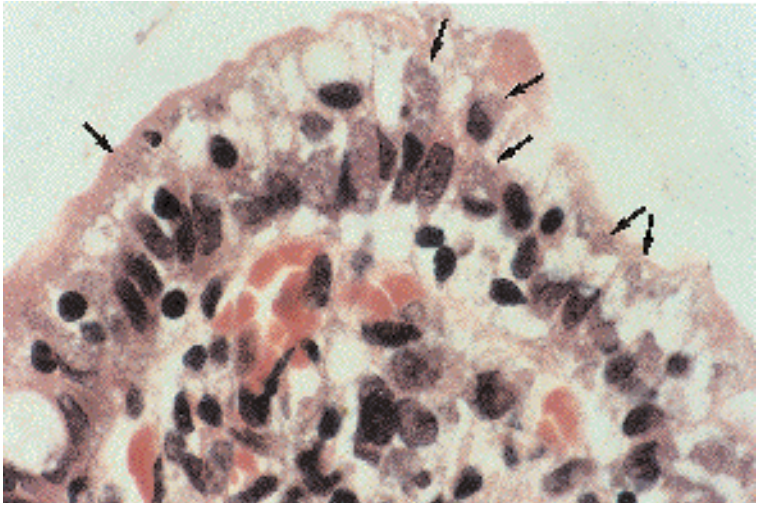

Figure 2. Distal duodenal biopsy stained with haematoxylin and eosin, showing multiple enterocytes infected with* Enterocytozoon bieneusi *(arrows). The spores are slightly refractile.

have occurred, and for this reason AIDS patients should be advised to boil all drinking water. However, more recently it has been shown that some strains seem to be unique to humans, and direct human-to-human transmission may be responsible for many human infections. Either small bowel or large bowel infection can occur (*Figure 3*) and some patients have infection in both sites.

Diagnosis is usually straightforward from stool microscopy, but occasionally biopsies are helpful. In patients with a CD4 count above 200/µl the infection usually resolves spontaneously, but in more immunocompromised patients spontaneous remission is uncommon. Treatment with paromomycin provides effective palliation for the diarrhoea in many cases (White et al, 1994), although colicky abdominal pain can occur. The infection is not eliminated by paromomycin and the mechanism of action of the drug is unclear.

Infection with either cryptosporidia or microsporidia can be apparently cured by immune reconstitution with potent antiretroviral treatment (Carr et al, 1998). However, it is unlikely that either infection is completely eradicated as relapse can occur once the CD4 count declines.

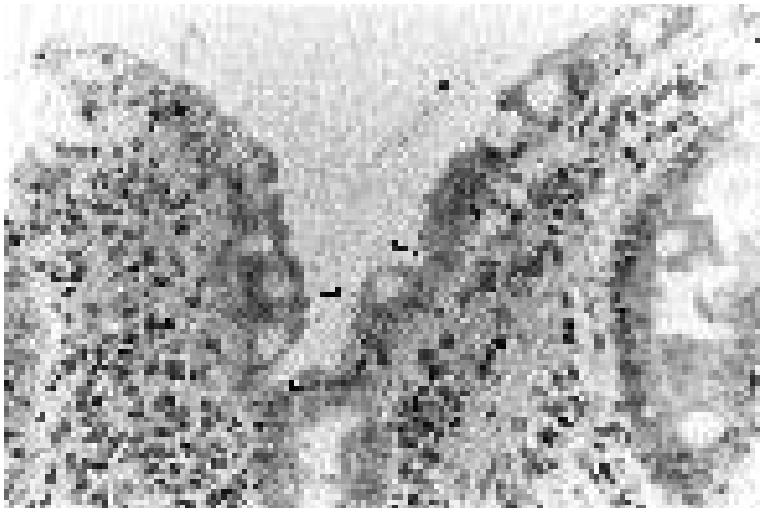

Figure 3. Small bowel infection with Cryptosporidium parvum *(arrows).*

TABLE 1.
Relapse of cytomegalovirus (CMV) disease of the gut following induction therapy in patients who did and did not receive maintenance therapy

		Maintenance (*n*=10)	No maintenance (*n*=39)
No. (%) relapsing	With gastrointestinal CMV	2 (20)	18 (46)
	With retinitis	5 (50)	20 (51)
Median time to relapse (weeks)		16	13
Median relapse-free survival (weeks)		17	17
Median overall survival (weeks)		31	38

From Blanshard et al (1995)

Cytomegalovirus: CMV most commonly infects the colon in patients with a CD4 count of less than 100/µl. There may be preceding or simultaneous CMV retinitis, and ophthalmological assessment is essential. CMV causes a spectrum of endoscopic appearances, ranging from large deep penetrating ulcers, to small superficial ulcers, submucosal haemorrhage, patchy mild colitis or even virtually normal mucosa with positive biopsies. The diagnosis is by endoscopic biopsy which demonstrates the characteristic owls-eye inclusions. However, the cytopathic changes can be patchy and may be missed unless multiple biopsies are taken. Immunohistochemical staining for CMV may increase the sensitivity of diagnosis. More rarely CMV infection of the small bowel can be a cause of diarrhoea.

Treatment of gastrointestinal CMV is with either ganciclovir or foscarnet, both requiring intravenous infusion twice daily for 2–4 weeks. Both drugs are equally effective but have a different spectrum of toxicity: bone marrow suppression with ganciclovir and renal impairment and penile ulceration with foscarnet (Blanshard et al, 1995). Relapse of the gastrointestinal disease or development of retinitis occurs in the majority of patients following successful treatment, usually within a few months, regardless of whether maintenance treatment is given (*Table 1*).

Adenovirus: Adenovirus can infect the large bowel in AIDS patients. This may be associated with diarrhoea and a histological colitis (Maddox et al, 1992). The sigmoidoscopic appearances are variable and usually limited to mild erythema, granularity or contact bleeding of the mucosa. As yet there is no antiviral treatment available.

Mycobacterium avium intracellulare: MAI infection usually only occurs in patients with a CD4 count less than 100/µl. The organism is acquired from the environment and disseminates from the gastrointestinal or respiratory tract causing a systemic illness with fever, anaemia, weight loss, diarrhoea and hepatomegaly. Diagnosis is by culture of blood, stool, bone marrow or liver biopsy and treatment requires two or more antimycobacterial drugs (for example azithromycin, clarithromycin, ethambutol, clofazamine, rifampicin, rifabutin, ciprofloxacin or amikacin). Unfortunately, while treatment usu-

ally results in remission of the systemic symptoms, diarrhoea rarely resolves. MAI may be prevented by primary prophylaxis with rifabutin, which is now recommended for all patients with a CD4 count of less than 100/μl.

Recently *Cyclospora* has been discovered as a cause of diarrhoea in AIDS patients (Pape et al, 1994). The organisms in the stool superficially resemble cryptosporidia on acid-fast staining but are larger (8–9 μm compared to 5 μm).

PATHOGEN-NEGATIVE DIARRHOEA

In a small proportion of AIDS patients with chronic diarrhoea no infection will be found despite intensive investigation. Some of these will have small bowel lymphoma or very extensive intestinal Kaposi's sarcoma, but for the remainder the diarrhoea may resolve and their prognosis is not affected. Only 1–2% of AIDS patients have severe debilitating chronic diarrhoea for which no cause can be found (Blanshard and Gazzard, 1995).

For some patients, optimization of their antiretroviral treatment, and giving such treatment as there is for their enteric pathogen does not result in resolution of the diarrhoea and symptomatic treatment with antidiarrhoeals is required to preserve some quality of life. The author recommends a stepwise approach, starting with imodium or diphenoxylate, then codeine phosphate up to 120 mg four times daily and, if this fails, oral morphine. Octreotide has been advocated as a treatment for refractory AIDS-associated diarrhoea but has been shown to be no better than placebo (Simon et al, 1995).

LIVER DISEASE

In early HIV infection, abnormalities of liver function are usually due to infection with hepatitis B or C virus, or drug-related hepatotoxicity.

Later, the liver may be involved as part of a disseminated infection with an opportunistic pathogen or malignancy (*Table 2*). Blood culture or bone marrow aspiration may give the diagnosis, but liver biopsy for histology and culture is indicated if clotting permits.

Baciliary peliosis hepatitis presents with fever, hepatosplenomegaly, cutaneous and bony lesions (Perkocha et al, 1990). Liver biopsy shows dilated venous lakes in the hepatic parenchyma and bacteria may be visible if silver stains are used. The responsible organism is *Bartonella quintana* or *Bartonella henselae*.

There is no evidence that hepatitis A is more severe than in the general population.

Reactivation of latent hepatitis B infection can occur as HIV infection progresses and surface antigen can reappear in previously negative individuals. However, the hepatitis is not more severe in patients with AIDS, as much of the liver damage in hepatitis B infection is thought to be immunologically mediated. Interferon alpha is not usually indicated for the treatment of hepatitis B in AIDS patients as hepatitis B virus surface antigenaemia does not adversely affect prognosis.

Hepatitis C infection is particularly common in haemophiliacs and patients who are or have been injecting drug users and can cause rapidly progressive liver disease. Interferon alpha may be of benefit in patients who are not too severely immunosuppressed, but in later stage disease interferon is not indicated as the patient's prognosis is more affected by opportunistic infections.

SCLEROSING CHOLANGITIS

AIDS-related sclerosing cholangitis, also known as AIDS cholangiopathy, is a disorder characterized by stricturing and beading of the intrahepatic bile ducts, with or without stricturing or dilatation of the extrahepatic bile ducts and papillary stenosis (*Figure 4*). Right

TABLE 2.
Causes of parenchymal liver disease in patients with human immunodeficiency infection

Hepatotrophic viruses	Hepatitis A
	Hepatitis B
	Hepatitis C
	Delta virus
Drugs	Sulphonamides
	Zidovudine
	Protease inhibitors
Bacillary peliosis hepatitis	
Systemic infections	*Mycobacterium tuberculosis*
	Mycobacterium avium intracellulare
	Cytomegalovirus
	Cryptococcus
	Histoplasma
	Coccidiomycosis
	Candida
	Pneumocystis carinii
	Microsporidia
Disseminated malignancy	Lymphoma
	Kaposi's sarcoma

upper quadrant pain and a raised alkaline phosphatase level are the usual presenting features; jaundice and itch are uncommon. In many cases, infection of the biliary epithelium with *Cryptosporidium*, microsporidia or CMV is responsible, but treatment of the infection does not usually alter the course of the disease. It is unclear whether sphincterotomy in those cases where there is papillary stenosis has any effect on symptoms or liver function tests. AIDS-related sclerosing cholangitis can cause considerable morbidity as a result of pain, but does not adversely affect survival (Forbes et al, 1993). HM

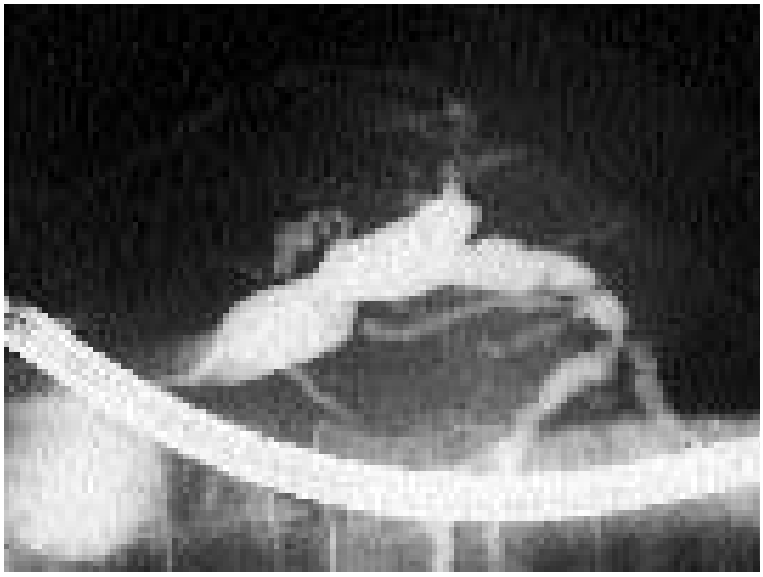

Figure 4. Endoscopic retrograde cholangiogram illustrating acquired immunodeficiency syndrome-related sclerosing cholangitis. Note the dilated common bile duct resulting from papillary stenosis, with irregular stricturing of the intrahepatic ducts. This case was caused by cryptosporidium, which was identified in the bile as well as the stools.

KEY POINTS

- The advent of potent antiretroviral therapy has changed the spectrum of human immunodeficiency virus-related gastrointestinal disease as most symptoms occur in the most severely immunocompromised patients.
- Oesophageal symptoms are most commonly caused by *Candida;* if they do not respond to antifungals then endoscopy is required to look for other opportunistic infections.
- Diarrhoea is particularly common in gay men and patients with low CD4 counts. It is almost always the result of a gut pathogen.
- Extensive investigation may be required and the close support of the microbiology and histopathology departments is essential as special diagnostic techniques may be required.
- Gut pathogens should be treated by optimizing antiretroviral treatment as well as specific treatment directed at the pathogen.

Anwar-Bruni DM, Hogan SE, Schwartz DA, Wilcox CM, Bryan RT, Lennox JL (1996) Atovaquone is effective treatment for the symptoms of gastrointestinal microsporidiosis in HIV-1 infected patients. *AIDS* **10:** 619–24

Blanshard C, Gazzard BG (1993) The incidence and cause of transient and persisting diarrhoea in relation to CD4 lymphocyte count in HIV infected individuals. *Eur J Gastro Hepatol* **5:** 823–8

Blanshard C, Gazzard BG (1995) The natural history and prognosis of diarrhoea of unknown cause in HIV seropositive individuals. *Gut* **6:** 283–6

Blanshard C, Dowell S, Ellis DS, Gazzard BG (1992a) Treatment of small intestinal microsporidiosis with albendazole in patients with AIDS. *AIDS* **6(3):** 311–3

Blanshard C, Jackson AM, Shanson DC, Francis N, Gazzard BG (1992b) Cryptosporidiosis in HIV-seropositive patients. *Q J Med* **85:** 813–23

Blanshard C, Benhamou Y, Dohin E, Lernestedt JO, Gazzard BG, Katlama C (1995) Treatment of HIV-related CMV infection of the gut with foscarnet and ganciclovir: a randomised comparison. *J Infect Dis* **172:** 622–8

Carr A, Marriott D, Field A, Vasak E, Cooper DA (1998) Treatment of HIV-1 associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. *Lancet* **351:** 256-61

Dieterich DT, Wilcox CM (1996) Diagnosis and treatment of oesophageal diseases in patients with HIV infection. *Am J Gastroenterol* **91:** 2265–9

Forbes A, Blanshard C, Gazzard B (1993) The natural history of AIDS-related sclerosing cholangitis: a study of 20 cases. *Gut* **34:** 116–21

Maddox A, Francis N, Moss J, Blanshard C, Gazzard BG (1992) Adenovirus infection of the large bowel in HIV positive patients. *J Clin Pathol* **45:** 684–8

Palella FJ Jr, Delaney KM, Moorman AC et al (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* **338:** 906–8

Pape JW, Verdier RI, Boncy M, Boncy J, Johnson WD (1994) Cyclospora infection in adults infected with HIV. Clinical manifestations, treatment and prophylaxis. *Ann Intern Med* **121:** 654–7

Peacock CS, Blanshard C, Tovey DG, Ellis DS, Gazzard BG (1991) The histological diagnosis of intestinal microsporidiosis in patients with AIDS. *J Clin Pathol* **44:** 558–63

Perkocha LA, Geaghan SM, Yen TS et al (1990) Clinical and pathological features of bacillary peliosis hepatitis in association with human immunodeficiency virus infection. *N Engl J Med* **323:** 1581–6

Sharpstone D, Rowbottom A, Francis N, Tovey G, Ellis D, Barret M, Gazzard B (1997) Thalidomide: a novel therapy for microsporidiosis. *Gastroenterology* **112:** 1823–9

Simon DM, Cello JP, Valenzuela J et al (1995) Multicentre trial of octreotide in patients with refractory acquired immunodeficiency syndrome-associated diarrhoea. *Gastroenterology* **108:** 1753–60

Snijders F, Kuiper EJ, De Wever B, van der Hoek L, Danner SA, Dankert J (1997) Prevalence of *Campylobacter*-associated diarrhoea among patients infected with human immunodeficiency virus. *Clin Infect Dis* **24:** 1107–13

van Gool T, Snijders F, Reiss P et al (1993) Diagnosis of intestinal and disseminated microsporidial infections in patients with HIV by a new rapid fluorescence technique. *J Clin Pathol* **46:** 694–9

Weber R, Bryan RT, Owen RL et al (1992) Improved light microscopical detection of microsporidia spores in stool and duodenal aspirates. *N Engl J Med* **326:** 161–8

White AC, Chappell CL, Hayat CS, Kimball KT, Flanigan TP, Goodgame RW (1994) Paromomycin for cryptosporidiosis in AIDS. A prospective, double blind trial. *J Infect Dis* **18:** 447–9