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Gastrointestinal manifestations of HIV infection

D Sharpstone, B Gazzard

The harrowing picture of emaciated terminally ill AIDS patients is a reminder of our lack of understanding of immunological mechanisms that normally control opportunistic infections. Many gastrointestinal pathogens in patients with AIDS are resistant to treatment and lead inexorably to weight loss and death. Although knowledge of the pathogenesis and clinical significance of weight loss has improved considerably, this has not yet led to a sustained effort to improve nutritional status during early stages of disease.

Most of the morbidity and mortality of late AIDS is associated with gastrointestinal disease. Whilst oesophageal candidosis responds readily to treatment and cytomegalovirus enteritis may be cleared by antiviral agents, the two commonest protozoal pathogens—*Microsporidia* and *Cryptosporidia*—cannot be eradicated. These protozoa cause disruption of small-bowel villus architecture by unknown mechanisms and severe malabsorption, maldigestion, and diarrhoea.

Weight loss is a major contributor to death in most patients with AIDS and is commonly caused by protozoal gut infection. The host metabolic response to these infections is typical of starvation and patients are likely to respond to the provision of additional calories, ideally by the enteral route. By contrast, weight loss associated with other opportunistic infections—*Mycobacterium avium intracellulare* and cytomegalovirus—is characterised by cachexia and is unlikely to respond to simple refeeding.

Oesophageal disorders

The commonest cause of oesophageal symptoms is candidosis; odynophagia or dysphagia with oral candidosis is an AIDS-defining diagnosis and can be treated empirically with a systemic azole. The second most frequent cause is cytomegalovirus (CMV), which produces either diffuse oesophagitis or discrete ulceration. The aetiology of these lesions can be confirmed by biopsy of the centre of ulcerated areas. Detection of CMV inclusion bodies is enhanced by immunoperoxidase staining. Oesophagoscopy occasionally reveals vesicles typical of herpes simplex oesophagitis, diagnosed either by biopsy or smears from brushings showing typical giant cells. As many as 10% of oesophageal ulcers leading to dysphagia are idiopathic, possible causes being unknown opportunistic viruses or HIV itself.¹ These ulcers may respond to thalidomide.

Diarrhoea

Pathogenesis

HIV was initially believed to cause intestinal symptoms since HIV-seropositive individuals free from intestinal pathogens commonly have diarrhoea. However, the frequency of "pathogen-negative diarrhoea" depends on

the extent of the diagnostic investigations and the definition of diarrhoea. In a prospective study² of pathogen-negative diarrhoea, follow-up revealed an unsuspected pathogen in only a minority. Most patients had low-volume diarrhoea that either resolved spontaneously or was controlled with antimotility agents, a response that accords with the features of irritable bowel syndrome. HIV-seropositive persons free from intestinal pathogens do have minor abnormalities of villus architecture, characteristically a mild villus atrophy associated with either crypt hypoplasia or hyperplasia.³ These minor abnormalities are unlikely to cause diarrhoea since they occur in symptom-free individuals and are associated either with no or with very mild malabsorption of carbohydrates.⁴ However, there is a consistent increase in small-bowel permeability in HIV-seropositive individuals;⁵ this functional abnormality and the minor structural abnormalities of the small bowel mucosa may be due to the immunological changes produced by HIV infection of lamina propria lymphocytes. Activated T cells cause villus atrophy in fetal gut explants,⁵ and HIV causes activation of these cells. HIV can be identified in the lamina propria of both the large and small intestine but its detection or quantification is not related to diarrhoea.⁶ Whether HIV also infects small-bowel mucosal cells, as was initially shown by in-situ hybridisation, is unknown.⁷ Other possible mechanisms for villus damage include ingress of foreign antigens because of the increased permeability that sets in motion a vicious circle of release of cytokines and other inflammatory mediators. Alternatively, bacterial overgrowth in the small intestine of HIV-seropositive patients, as reported in some small studies, might produce an inflammatory response and villus atrophy.⁸ Bacterial overgrowth might occur because of the hypochlorhydria reported in AIDS patients.⁹ Hypochlorhydria is common in those with starvation and systemic infection¹⁰ and may therefore occur in advanced AIDS without any HIV-induced defects in gastric secretion. Neither hypochlorhydria nor bacterial overgrowth is a universal finding in patients with advanced HIV infection, so these mechanisms are unlikely to have an important role in villus atrophy.

Protozoal diarrhoea

Enteric protozoal infection is the commonest cause of diarrhoea in HIV-seropositive persons (table) and is associated with apoptosis, occasional crypt abscesses, and much more severe villus atrophy than that seen with HIV infection alone.¹⁸ Malabsorption and maldigestion increase bowel frequency. However, symptoms persist despite

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Pathogen	Mean prevalence (%) (range)
<i>Cryptosporidia</i>	19.6 (6.5-37.3)
<i>Microsporidia</i>	19.4 (2.0-39.0)
Cytomegalovirus enteritis*	20.1 (7.5-28.6)
<i>Mycobacterium avium-intracellulare</i>	9.3 (2.3-25.0)
<i>Giardia lamblia</i>	4.9 (1.5-11.6)
<i>Entamoeba histolytica</i>	2.6 (0.5-2)
<i>Campylobacter</i> spp	3.3 (0-10.6)
<i>Salmonella</i> spp	2.1 (0-7.6)
<i>Shigella</i> spp	1.9 (0-4.9)
<i>Clostridium difficile</i>	1.8 (0-7.1)
<i>Isospora belli</i>	1.5 (0-3.0)
Enteric viruses†	3.8 (1.5-9.7)
Any pathogen isolated	67 (54.9-83.0)

*Oesophagitis, gastritis, duodenitis, or colitis. †Adenovirus, rotavirus, coronavirus, or small round structured virus. Compiled from references 11-17.

Table: Prevalence of gastrointestinal pathogens isolated from AIDS patients with diarrhoea

starvation, and diarrhoea is often out of proportion to the mucosal abnormalities, so a secretory component is likely. A secretory response was shown in isolated segments of human jejunum exposed to faeces from calves infected with *Cryptosporidia*¹⁹ but not in patients with moderately increased stool volumes due to cryptosporidiosis.²⁰

Decreased intestinal transit time may exacerbate diarrhoea in protozoal infection,²¹ but whether this is a primary motility defect or a consequence of malabsorption or enteric nerve damage is unclear.²² Another possibility is that motility changes or nerve damage are mediated by nitric oxide release as a result of stimulation of nitric oxide synthase in macrophages infected by HIV or opportunistic organisms; this possibility remains unexplored.

Changes in the immunological responses in the gut mucosa allow the persistence of protozoal infection in HIV-seropositive individuals, and abnormal immune responses themselves may be important in the pathogenesis of diarrhoea. The CD4 lymphocyte population of the lamina propria in HIV-seropositive patients shows a disproportionate reduction compared with the circulating CD4 count.²³ Experiments in immunocompromised mice have shown that CD4-positive cells are essential for the eradication of *Cryptosporidia*.²⁴ CD8 responses may be important in controlling infection in CD4-count-depleted mice, and interferon-gamma released from macrophages may also have a role.²⁵ Altered CD8 or macrophage responses in HIV-seropositive individuals who are unable to mount a CD4 response to cryptosporidial infection may lead to aberrant cytokine release and consequent intestinal damage. Increased concentrations of tumour necrosis factor-alpha have been reported in the faeces²⁶ but not in the mucosa of patients with protozoal diarrhoea.²⁷ Studies of the complex balance between various cytokines and their tissue receptors are awaited.

Diagnosis of causes of diarrhoea

Stool analysis is the initial investigation for HIV-seropositive subjects with diarrhoea and three samples will identify about 80% of pathogens.²⁸ In moderately immunosuppressed patients (CD4 >200/ μ L) stool analysis is probably the only investigation necessary. Opportunistic viruses and protozoa are uncommon, although infection with *Cryptosporidia* does occur but is transient, and *Giardia* infection that may be difficult to diagnose at all stages of HIV infection is often treated empirically.

Stool analysis should include techniques that reliably diagnose *Microsporidia*. The spores of this organism

fluoresce with agents such as Calcofluor,²⁹ thereby providing an excellent screening test. Results can be confirmed with Giemsa staining. *Cryptosporidia* in the stool is diagnosed by a modified Ziehl-Neelsen or auramine stain. Enteric bacteria are usually detected by routine stool cultures but are occasionally found only in the blood.³⁰ Stool culture of *Mycobacterium avium intracellulare* is tedious and of uncertain pathogenic significance since colonisation can occur without diarrhoea.

The value of stool electron microscopy for enteroviruses is debatable since in some studies these organisms have a similar prevalence in individuals with solid stools and in those with diarrhoea.³¹ Detection is of limited value because enteroviruses produce a self-limiting infection, even in most HIV-seropositive persons, and are untreatable.

Mucosal biopsy: Although diagnosis by stool analysis alone has been suggested by Johanson and Sonnenberg,³² this study may have overestimated the value of symptomatic treatment and ignored the possibility that cytomegalovirus infection sometimes responds to therapy. Gut biopsy is the only way to diagnose infection with CMV or adenovirus. Infections are commonly found in the large intestine, and sigmoidoscopy with rectal biopsies is probably the best initial invasive gastroenterological investigation in patients with diarrhoea. 10-30% of cases of CMV colitis affect only the right side of the colon or small intestine, so colonoscopy or small-intestinal biopsy may be indicated in individuals with persistent diarrhoea and negative rectal biopsy.³³

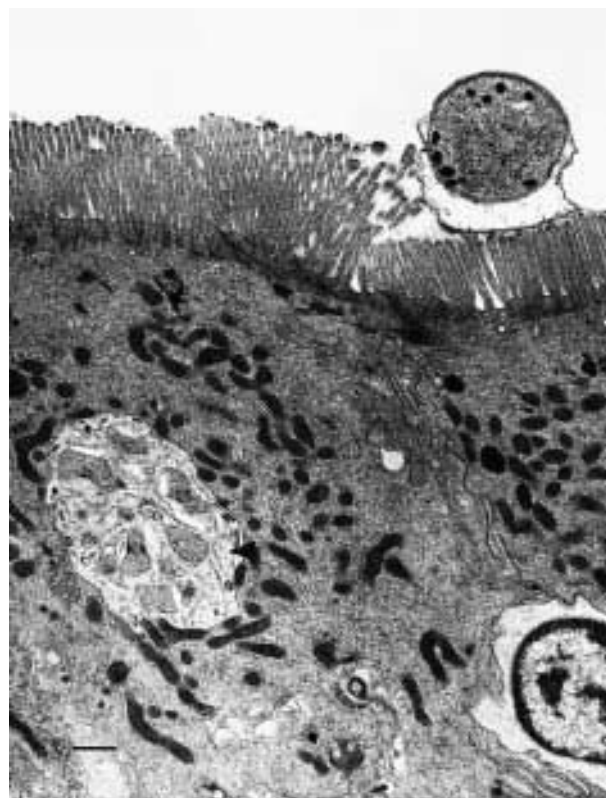


Figure: Electronmicrograph of duodenal mucosa enterocytes from patient with AIDS-related diarrhoea showing a plasmodium of *Enterocytozoon bienewisi* (arrowed) and an oocyst of *Cryptosporidium parvum* (top right)

Identification bar= 1 micron. Courtesy of G Tovey and Dr D Ellis, London School of Hygiene and Tropical Medicine.

Cryptosporidia may not always take up appropriate stains in the stool and some infections are diagnosed only by histological examination of small or large bowel biopsy specimens. Histological examination of duodenal biopsy specimens may also reveal previously unsuspected *Microsporidia*, *Giardia*, *M avium intracellulare*; or *Isospora*. Ultrastructural examination of enteric biopsy specimens by electromicroscopy is not done routinely but enables speciation of organisms such as *Microsporidia* and maybe a useful addition to light microscopy (figure).

Analysis of six stool samples and histological examination of small and large bowel biopsy specimens detect more than 90% of infectious causes of diarrhoea in HIV-seropositive individuals.²⁸ Most individuals in whom no pathogens are found by these initial investigations have minor symptoms that usually resolve spontaneously. A few have continued large-volume diarrhoea, and in some of these widespread Kaposi's sarcoma of the gut or lymphoma is subsequently diagnosed.²

Management of diarrhoea

After stool analysis, acutely ill individuals with diarrhoea should be treated with ciprofloxacin, to which most enteric bacteria in HIV-seropositive individuals are sensitive.

In those with chronic diarrhoea, antimotility agents reduce symptoms. Oral rehydration therapy may also be important to maintain electrolyte balance. The somatostatin analogues octreotide and vapreotide are used in HIV-seropositive individuals with diarrhoea because of a motility effect and possibly because HIV has aminoacid sequences similar to vasoactive intestinal peptide (VIP) and may induce diarrhoea by upregulating VIP receptors.³⁴ Increased concentrations of VIP have been shown in some patients with pathogen-negative diarrhoea, in whom octreotide has likewise been successful.³⁵ Somatostatin analogues are most effective for pathogen-negative diarrhoea and less so in protozoal diarrhoea, with one placebo-controlled study showing no effect.³⁶ These expensive agents are unlikely to have a wide role in the treatment of HIV-related diarrhoea.

Microsporidiosis: Two genera of *Microsporidia* are associated with diarrhoea. *Enterocytozoon bienersi* is found only in human beings. There is no known effective treatment, although uncontrolled studies suggest that some patients may respond to albendazole,³⁷ thalidomide,³⁸ or atovaquone.³⁹ *Encephalitozoon* spp are much less commonly associated with diarrhoea, but infection with these organisms can also cause disseminated disease; organisms are eradicated by albendazole, with resolution of symptoms.

Cryptosporidiosis: There are many anecdotal reports of treatment for cryptosporidiosis that are difficult to interpret in view of the variable natural history of this infection. In at least a third of patients, diarrhoea resolves spontaneously, especially in those with an initial CD4 count above 200/ μ L. Investigation of suitable therapeutic agents is hampered by inability to culture the organism in vitro and the major differences between animal models and human infection. Although many agents have been used, the only one with proven efficacy is paromomycin, which reduces stool volumes by about 50%.⁴⁰ Quantitative stool analyses have shown some reduction in oocyst excretion with therapy but the organism is seldom

eradicated.⁴¹ Because therapy of this infection is so difficult, primary prophylaxis would be a highly desirable goal. Human cryptosporidiosis is a waterborne infection. Since the minimum infectious dose is low—between one and five oocysts in gnotobiotic animals⁴² and 20–50 oocysts in healthy human beings⁴³—standard screening tests of metropolitan water supplies may not be sensitive enough for detection. Boiling water eliminates infective oocysts, so this strategy is sensible for HIV-seropositive patients with CD4 counts of less than 200/ μ L.

Cytomegalovirus enteritis: The treatment of cytomegalovirus enteritis remains controversial. Both ganciclovir and foscarnet reduce symptoms and improve macroscopic and microscopic appearances of the colon with 3 weeks' therapy.⁴⁴ However, relapse with a median time of 12 weeks is very common. Both initial treatment and the decision to give maintenance therapy will therefore depend on the initial severity of symptoms. Since diagnosis of cytomegalovirus enteritis is improving, patients with milder symptoms are being detected and the quality of life with treatment—anti-CMV agents have to be given intravenously and have considerable toxicity—may not be enhanced compared with no therapy. Whether such patients left untreated will develop complications of CMV enteritis such as toxic dilation and perforation, which were common in the early years of the epidemic, remains to be determined. Oral ganciclovir in a high dose to overcome problems of bioavailability may have a limited role as primary prophylaxis in preventing the development of CMV disease. Nevertheless, such therapy has major toxicity, only limited benefit, and is extremely expensive. Widespread use of primary prophylaxis must await the development of more effective agents or of other markers that allow better prediction of patients who are most likely to develop CMV disease.

Mycobacterium avium-intracellulare (MAI): About 5% of severely immunosuppressed HIV-seropositive patients have MAI-induced diarrhoea.⁴⁵ Primary prophylaxis with rifabutin or clarithromycin may reduce the incidence of MAI but established small-bowel infection necessitates treatment with conventional quadruple therapy. Such treatment must include the most effective agents—clarithromycin or azithromycin. Resistance to these drugs will probably be limited by the addition of rifabutin and their efficacy improved by ethambutol.

Wasting

Weight loss is a common feature of late HIV infection. Initially wasting was thought to be a feature of HIV infection per se.⁴⁶ However, although there is a slight increase in resting energy expenditure (REE) in individuals at most levels of immunosuppression, weight and lean body mass are normal unless an opportunistic infection supervenes.⁴⁷ The pattern of weight loss characteristic of starvation, with decreased REE and relative preservation of lean body mass, is seen with enteric protozoal infection.⁴⁸ The starvation response is probably caused by a combination of voluntary reduction of intake to reduce diarrhoea and anorexia related to malabsorption. Certain opportunistic infections, especially *M avium intracellulare* and CMV, produce a cachectic response in which the REE is further raised and there is a more pronounced loss of lean body mass, likely to be

related to inappropriate cytokine release.⁴⁸

Although increase in fat mass may improve body image, repletion of lean body mass is probably required to improve locomotor function and many aspects of quality of life. HIV-seropositive individuals losing weight because of starvation are likely to respond to food supplements given orally, parenterally, or enterally via a nasogastric tube or percutaneously by gastroenterostomy tube. Such patients may also benefit from appetite stimulants. However, refeeding is likely to be ineffective in those with cachexia, who may improve lean body mass in response to anabolic agents (eg, recombinant human growth hormone).⁴⁹

Abdominal pain

CMV infection is associated with an arteritis and the consequent ischaemia may be associated with acalculous cholecystitis or appendicitis. CMV colitis commonly gives rise to abdominal pain with bloody diarrhoea and rebound tenderness. The other origin of abdominal pain unique to HIV-seropositive patients is an AIDS-related sclerosing cholangitis caused by various opportunists including *Microsporidia*, CMV, and *Cryptosporidia*.⁵⁰ This condition is associated with sclerosis of both the intrinsic and the extrinsic hepatic system and with changes in the pancreatic duct. Sclerosing cholangitis may also be common in those without pain, but it is usually the discomfort that leads to investigation. Since the natural history of this pain is variable, how frequently sphincterotomy improves symptoms is unclear.

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Review article

Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications

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Summary

Background Low adherence of patients to prescribed, self-administered medical interventions is ubiquitous. Low adherence limits the benefits of current medical care. Efforts to assist patients to follow treatments might improve the efficiency of care and substantially enhance benefits. Our objective was to summarise the results of randomised controlled trials (RCTs) of interventions to help patients follow prescriptions for medications.

Methods A previous systematic review was updated through computerised searches in Medline, International Pharmaceutical Abstracts, Psycinfo, and HSTAR online databases; bibliographies in articles on patient adherence; articles in the reviewers' personal collections; and contact with authors. Articles were judged of interest if they reported original data concerning an unconfounded RCT of an intervention to improve adherence with prescribed medications, with one or more measure of medication adherence, one or more measure of treatment outcome, at least 80% follow-up of each group studied, and, for long-term treatments, at least 6 months of follow-up for studies with positive initial findings. Information on study design features, interventions and controls, and findings were extracted by one reviewer (RK) and checked by the other two reviewers.

Findings 1553 relevant citations and abstracts were screened, 252 full text articles were reviewed in detail, and 13 RCTs met all criteria. The studies were too disparate in clinical problems, adherence interventions, measures and

reporting of adherence, and the clinical outcomes studied to warrant meta-analysis. Seven of 15 interventions were associated with improvements in adherence and six interventions led to improvements in treatment outcomes. For short-term treatments, one study showed an effect on adherence and outcome of counselling and written information. The interventions that were effective for long-term care were complex, including various combinations of more convenient care, information, counselling, reminders, self-monitoring, reinforcement, family therapy, and other forms of additional supervision or attention. Even the most effective interventions did not lead to substantial improvements in adherence.

Interpretation Although adherence and treatment outcomes can be improved by certain—usually complex—interventions, full benefits of medications cannot be realised at currently achievable levels of adherence. It is time that additional efforts be directed towards developing and testing innovative approaches to assist patients to follow treatment prescriptions.

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Introduction

Non-adherence with prescribed treatments is very common. Typical adherence rates for prescribed medications are about 50% with a range from 0% to over 100%.¹ To the extent that treatment response is related to dose, non-adherence reduces treatment benefits² and can bias assessment of the efficacy of treatments.³ With increasing numbers of efficacious self-administered treatments, the need is apparent for better understanding and management of non-adherence.

In previous reviews, we have examined the accuracy of clinical measures of non-adherence,⁴ interventions to improve attendance at appointments for medical services,⁵ and interventions to enhance medication adherence.⁶ In the last review some of the included trials were

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