4 Gastrointestinal opportunistic infections

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4.1 Methods

The PubMed database was searched under the following headings: HIV or AIDS and diarrhoea, oesophagitis, candida, *Clostridium difficile*, cryptosporidium, cyclospora, cytomegalovirus, entamoeba, giardia, herpes, isospora, microsporidia, mycobacteria, parasites, salmonella, shigella, strongyloides.

4.2 General overview

Gastrointestinal symptoms are among the most frequent problems in patients with HIV disease, and diarrhoea may be caused by a wide variety of organisms (Table 4.1). Symptoms may arise from any part of the GI tract including the mouth, throat, oesophagus, stomach, small and large intestine, liver, gall bladder, rectum and anus. The spectrum of disease has changed with the introduction of HAART with a fall in the overall incidence of opportunistic infections and an increase in medicine related side-effects and of conditions found in the HIV-seronegative population. If a cause is not apparent consultation with a gastroenterologist with an interest in HIV related disease of the GI tract is indicated since HIV-seropositive individuals are also susceptible to many of the same conditions as the HIV-seronegative population. Coinfection with hepatitis B or C virus is not covered in these guidelines as it is the subject of separate guidelines [1].

4.3 Oesophagitis

- Oesophagitis should be treated empirically with fluconazole and oesophagoscopy should be performed if symptoms fail to settle initially (category Ib recommendation).
- Specific treatment for oesophagitis in cases that fail to settle with empirical therapy should be directed at the cause identified by biopsy, culture and antimicrobial sensitivity testing (category III recommendation).

Oesophagitis should be suspected in patients who experience pain on swallowing, with or without symptoms of reflux or dysphagia. The most common causative organisms are *Candida* spp. Persistent or recurrent oesophageal candidiasis has decreased in the HAART era and most often indicates failing or poor HIV viral control [2,3]. Treatment and prophylaxis with fluconazole and alternative agents have been subjects of a recent Cochrane review [4]. This review showed that fluconazole was superior to nystatin in terms of clinical cure and to clotrimazole in terms of mycological cure, while also showing that itraconazole was similar to fluconazole in its efficacy. Fluconazole should not be used in pregnancy.

The other major HIV-related infectious causes of oesophagitis include herpes simplex and cytomegalovirus infections, which cause ulceration and may coexist with candidiasis, especially if CD4 counts are < 100 cells/μL. Idiopathic ulcers are also common. Other causes of oesophageal symptoms include pill-associated ulcers. These have been associated with a number of medications, most commonly in the mid oesophagus. Doxycycline and related antimicrobials, non-steroidal anti-inflammatory drugs, potassium supplementation and iron tablets are the commonest causes likely to be encountered in HIV-seropositive patients [5,6].

A randomised trial has demonstrated that initial empirical therapy for candidiasis is a reasonable initial approach in uncomplicated oesophagitis [7]. Oesophagoscopy should

Table 4.1 Major causes of HIV-related diarrhoea

Bacteria	Parasites and fungi	Viruses	Non-infectious
Campylobacter spp	*Cryptosporidium* spp	Cytomegalovirus	Antiretroviral therapy
Clostridium difficile	*Cyclospora cayetanensis*	Herpes simplex viruses	*Kaposi's sarcoma*
Escherichia coli	*Giardia lamblia*	Rotavirus	Lymphoma: Hodgkin and non-Hodgkin
Salmonella spp	*Entamoeba histolytica*	Norovirus	
Shigella spp	*Isospora belli*		
Mycobacterium tuberculosis	*Microsporidia*		
Mycobacterium avium-intracellulare complex	*Strongyloides stercoralis*		
Mycobacterium kansasii			

be performed if symptoms have failed to resolve after an empirical trial of azoles. Adequate and appropriate specimens must be taken to enable histological and virological diagnoses, together with cultures and anti-fungal susceptibility testing for the identification of azole-resistant *Candida* strains.

Azole-sensitive strains should be treated with fluconazole 50–100 mg po for 7–14 days (category Ib recommendation), which is the preferred azole due to experience and superior bioavailability in comparison to itraconazole [8]. Alternatives include caspofungin, 70 mg loading dose then 50 mg once a day iv [9], or liposomal amphotericin B 3 mg/kg once a day iv [10,11], used for the same duration as fluconazole. Of these, the side-effect profile of caspofungin and its efficacy in clinical trials make it the preferred agent when azole therapy cannot be used (category III recommendation).

In most cases primary and secondary prophylaxis for oropharyngeal and oesophageal candidiasis has been largely abandoned due to the rapid emergence of resistance [7]. One randomized clinical trial suggests that for individuals with very frequent symptomatic relapses, continuous fluconazole treatment (at 200 mg per day) is more effective than intermittent treatment at preventing relapses and reducing colonization [12]. In this study the intermittent treatment group required a median of four treatment courses per year and had a high incidence of azole resistance, which was comparable to the group on continuous treatment. Intermittent self treatment with fluconazole may be appropriate for individuals with persistently low CD4 cell counts and less frequent relapses and is likely to be the most appropriate strategy for most individuals with a history of relapsing oropharyngeal candidiasis in the HAART era where secondary prophylaxis should be reserved for select cases (category IV recommendation) [7,13].

CMV oesophagitis is treated with ganciclovir 5 mg/kg bd iv for 2–4 weeks, or until symptoms/signs have resolved (category III recommendation) [14,15]. Valganciclovir may be substituted for iv ganciclovir at 900 mg bd orally for some or all of the duration if symptoms are not severe enough to interfere with oral absorption on the basis of studies showing efficacy for CMV disease in transplant patients [16] but there is a paucity of data in HIV-related CMV disease of the gastrointestinal tract (category IV recommendation). Secondary CMV prophylaxis for oesophageal disease is not routinely indicated, unless there is concomitant ophthalmological disease. Herpes simplex oesophagitis is treated with aciclovir 5–10 mg/kg tid iv, followed by 400 mg five times a day orally for a total of 14 days (category III recommendation) [17] or oral valaciclovir 1 g bd orally (see 6 Herpes viruses for a discussion of prophylaxis of HSV). Foscarnet 90 mg/kg bd iv has been used in cases of ganciclovir-resistant CMV or 40 mg/kg bd or tid for aciclovir-resistant HSV [15].

- After presentation with infectious oesophagitis, early initiation of HAART should be considered (category IV recommendation) [18].

As elsewhere in these guidelines, early initiation of HAART is favoured on the basis that improved survival without AIDS progression or death has been seen when HAART is initiated within the first two weeks of treatment of the opportunistic infection [18]. This recommendation is extrapolated from a series in which most cases were not related to oesophageal opportunistic infection but is also supported by evidence of functional immunological benefits of antiretrovirals against organisms such as *Candida* spp. [19].

4.4 Diarrhoea

Diarrhoea is a common problem for people with HIV in both resource-poor and resource-rich settings, regardless of antiretroviral exposure. In the pre-HAART era, 30–70% of HIV-seropositive individuals experienced diarrhoea, and among European patients with CD4 counts <50 cells/μL, 49% would expect to develop diarrhoea within 1 year and 96% within 3 years [20]. In resource-poor areas, incidence and severity continue to be higher. Early clinical observations confirmed that diarrhoeal illness was linked to reduced quality of life and poorer survival [21]. Diarrhoea may be the presenting symptom of lymphoma and Kaposi's sarcoma, may affect up to 40–50% of those taking antiretroviral therapy (ART), can be induced by other medications and may be the result of an incompletely defined direct effect of HIV on the gut mucosa termed HIV-associated enteropathy [22–25]. For a list of some causes of diarrhoea in HIV-seropositive individuals see Table 4.1.

- Every effort should be made to confirm a specific diagnosis in patients with significant immunosuppression (category IV recommendation).

Various algorithms have been proposed for the investigation and/or empirical management of chronic HIV-related diarrhoea (three or more loose stools for 28 or more days) in Western [26–30] and tropical settings [31–33]. Parasitic causes are more likely in those with prolonged diarrhoea, considerable weight loss and CD4 count <100 cells/μL, and may coexist with CMV, mycobacterial or other infections.

4.4.1 Acute diarrhoea due to bacteria and viruses

4.4.1.1 Background and epidemiology. Acute diarrhoea is more common in people living with HIV, especially in those who are older and have lower CD4 cell counts. Evidence to confirm increased carriage and pathogenicity

of many of the causative viral and bacterial pathogens is sparse, once risk factors such as socioeconomic circumstances, travel and sexual behaviour are controlled for.

Few studies of HIV-related diarrhoea include investigation for viruses other than cytomegalovirus (CMV) and there is only anecdotal evidence of increased severity or frequency of most viruses associated with gastroenteritis in HIV, including noroviruses and rotavirus [20,21]. There have been reports implicating coronavirus, which may coexist with bacterial pathogens [26] in acute diarrhoea, and adenovirus, which may coexist with CMV in patients with chronic diarrhoea [27]. Herpes simplex infections (HSV-2 and HSV-1) cause relapsing and severe proctocolitis and should be treated with aciclovir 400 mg five times daily po or valaciclovir 1 g bd po for 7–14 days, while severe infection may necessitate aciclovir iv 5 mg/kg tid for the initial part of therapy [34]. Prophylaxis should be considered for recurrent disease [see 6.3 Herpes simplex virus (HSV) infection]. CMV colitis can present with acute diarrhoea and is specifically addressed later as a major opportunistic infection of the gastrointestinal tract. Sexually transmitted agents such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (including lymphogranuloma venereum) should be considered in susceptible individuals.

Invasive non-typhoidal salmonellosis (NTS) was recognized early in the HIV epidemic to be strongly associated with immunosuppression in Western [29–31,35,36] and tropical [32,33] settings, but there is no association between HIV and typhoid or paratyphoid. Patients with HIV and NTS infections present with febrile illness or sepsis syndromes and diarrhoea may be absent or a less prominent feature [37,38]. As in HIV negative individuals, other bacterial pathogens include *Clostridium difficile*, *Campylobacter* spp and *Shigella* spp.

C. difficile was the most common cause of diarrhoea in a US cohort study [28] and has been described in British and resource-poor settings [39–41]. It has been implicated in over 50% of cases of acute diarrhoea in studies spanning both the pre- and post-HAART eras. It is more common in those with AIDS-defining illness and, this is likely to reflect greater exposure to risk factors: hospitalization, broad-spectrum antimicrobial use, treatment for toxoplasmosis specifically and use of acid-lowering therapy, and attention to modifying these risk factors is likely to be essential to control of the infection in HIV-seropositive individuals [42,43].

4.4.1.2 Presentation. The clinical spectrum for other causes of acute diarrhoea ranges from asymptomatic infection to severe dehydration and death. Viral gastroenteritis typically presents with a short prodrome with mild fever and vomiting, followed by 1–4 days of non-bloody, watery diarrhoea. Viral gastroenteritis is usually self-limiting. Bacteria causing gastroenteritis may cause bloody diarrhoea and abdominal pain. Bacteraemia is more common, but still unusual, in HIV-related campylobacter [44] and shigella [45] infections.

Presenting symptoms of *Clostridium difficile* infection are similar to HIV-seronegative individuals [46]. Case series show that *C. difficile* infection is no more severe in HIV-seropositive individuals though case reports of complications such as toxic megacolon and leukaemoid reactions exist as in other populations [46–49].

- Stool and blood cultures should be included in the routine diagnostic work-up of diarrhoea in HIV (category IV recommendation).
- In the UK, C. *difficile* toxin assessment and/or culture should be carried out in all HIV-seropositive individuals presenting with acute diarrhoea (category IV recommendation).

4.4.1.3 Treatment. Supportive measures are the mainstay for viral gastroenteritis.

If a bacterial cause is suspected from the history, antimicrobial therapy may be indicated. Principles of therapy are as for HIV-seronegative individuals and acute bacterial diarrhoea in individuals with preserved CD4 counts (>200 cells/μL) does not usually require treatment (category IV recommendation). In general, when individuals present with acute bacterial diarrhoea and a CD4 count <200 cells/μL, therapy will be indicated (category IV recommendation). When indicated, the choice should be guided by *in vitro* sensitivity patterns and antimicrobial susceptibility testing should be requested if not routine. Whilst the majority of isolates will be sensitive to ciprofloxacin 500 mg bd po for 5 days there are increasing reports of resistance, in both *Campylobacter* spp and *Salmonella* spp. In addition, the relationships between fluoroquinolones and *C. difficile* infection and MRSA colonization are resulting in less empirical use of this agent. Treatment should therefore be reserved for confirmed cases, as guided by sensitivity testing. In exceptional cases where the patient presents with signs of sepsis or severe symptoms the benefits of empirical treatment may outweigh the potential risks (category IV recommendation).

For *C. difficile* infection the first step is to stop the aetiological antibiotic. The response to specific therapy with metronidazole 400 mg tid po for 10 days or to vancomycin 125 mg po qid for 7–10 days is similar in HIV-seropositive and HIV-seronegative individuals and complications do not appear to be more or less common in HIV [46]. First episodes of *C. difficile* infection should be treated with metronidazole with consideration of vancomycin for fulminant disease, relapsing disease or non-responsive infection (category IV recommendation), following the recommendations for treatment in HIV-seronegative populations outlined in

Department of Health guidelines [50]. Therapy is indicated for *C. difficile* infection regardless of the CD4 cell count.

- Acute bacterial diarrhoea in HIV-seropositive individuals with CD4 counts >200 cells/μL usually does not require treatment, but should be treated when the CD4 count is <200 cells/μL (category IV recommendation).
- Acute bacterial diarrhoea should be treated as per susceptibility tests and local guidance (category IV recommendation).
- *C. difficile* infection should be treated with metronidazole 400 mg tid po for 10 days with vancomycin reserved for severe, relapsing or metronidazole non-responsive infection (category IV recommendation).

4.4.1.4 Impact of HAART. Trimethoprim-sulphamethoxazole (TMP-SMX, co-trimoxazole) reduced the incidence of infectious diarrhoea in the pre-HAART era [51]. Retrospective studies suggest that introduction of antiretroviral therapy, including zidovudine monotherapy, has been more effective than targeted antimicrobial prophylaxis in preventing recurrence of nontyphoidal salmonella [52], and that duration of antimicrobial prophylaxis, with agents such as fluoroquinolones need not exceed 30 days in patients established on HAART [53]. The incidence of bacterial diarrhoea declined steadily after the introduction of HAART [28], therefore HAART is the mainstay of preventing bacterial diarrhoea (category III recommendation).

Table 4.2 Gastrointestinal presentations of CMV disease

Mouth	Visible ulcers
	Odynophagia
	Fever
	Malaise
Oesophagus	Dysphagia
	Retrosternal pain
	Odynophagia
	Anorexia
	Nausea
	Weight loss
	OGD may reveal classic large, shallow ulcers affecting the distal third of the oesophagus
	Fever
	Malaise
Gallbladder	Right upper quadrant pain
	Raised alkaline phosphatase level
	Sclerosing cholangitis seen at ERCP
Colon	Bloody diarrhoea
	Abdominal pain
	Anorexia
	Weight loss
	Haemorrhage
	Perforation
	Sigmoidoscopy may reveal ulceration
	Fever
	Malaise
Rectum	Blood-stained stool
	Rectal pain
	Ulceration may be seen on proctoscopy
	Fever
	Malaise

OGD, oesophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography.

4.4.2 Cytomegalovirus

4.4.2.1 Background and epidemiology. Cytomegalovirus (CMV) is a member of the herpes family of viruses, usually acquired during childhood. CMV infection remains dormant unless an individual becomes immunosuppressed, when reactivation of latent infection may occur [54,55]. In the pre-HAART era, retinitis was the most common presentation of CMV [56], followed by gastrointestinal disease (see Table 4.2 for a list potential clinical manifestations of CMV in the GI tract). Most of the data about incidence of CMV were obtained from populations with retinitis. The majority of affected individuals had CD4 counts <100 cells/μL, with 80% of episodes occurring in those with CD4 counts <50 cells/μL. Since the advent of HAART, CMV infection may occasionally occur as part of immune reconstitution syndromes, but the overall incidence of CMV in individuals living with HIV has dramatically reduced [57].

4.4.2.2 Presentation. CMV may affect all sections of the gut. Table 4.2 illustrates clinical presentation according to area affected.

4.4.2.3 Diagnosis. CMV viraemia, detected by polymerase chain reaction (PCR), may be positive in the absence of end-organ disease and several studies have shown this to be of negligible diagnostic use [58,59]. As indicated in Table 4.2, endoscopy may reveal classical CMV ulceration of the gut mucosa and biopsy with histopathological review may identify characteristic intranuclear and intracytoplasmic 'owl's eye' inclusions [60]. The absence of ulceration makes a diagnosis of CMV colitis very unlikely [61].

The culture of CMV from biopsy material is not sufficient for the diagnosis of gut infection as immunosuppressed individuals may shed the virus without intestinal disease.

4.4.2.4 Treatment

- First line treatment for CMV colitis is intravenous ganciclovir (5 mg/kg twice daily) for 14–28 days (category Ib recommendation).
- Immediate optimization of HAART should be considered (category IV recommendation).

CMV colitis has traditionally been treated with ganciclovir 5 mg/kg bd iv for 14–28 days [62]. Caution should be used in initiating treatment with the oral medication valganciclovir as there is a theoretical concern of decreased absorption, but HIV and non-HIV-related cases of CMV

colitis have been successfully treated [63]. Intravenous foscarnet (90 mg/kg twice daily) for 14–28 days is used as an alternative [64,65].

Therapeutic drug monitoring may be required to ensure adequate HAART absorption (category IV recommendation).

Chronic maintenance therapy is not routinely recommended in gastrointestinal disease unless patients relapse after induction therapy ceases [64]. All individuals with CMV involving the gastrointestinal tract should have prompt ophthalmological evaluation to exclude concomitant CMV retinitis and if this is present treatment and secondary prophylaxis should be initiated as recommended (see section 5.1 CMV retinitis).

4.4.2.5 Impact of HAART. Continuous use of effective HAART is required to prevent relapse.

4.4.3 Cryptosporidium spp

4.4.3.1 Background and epidemiology. Cryptosporidium, a protozoan parasite, was the most common pathogen in HIV-antibody-positive individuals with chronic diarrhoea in the pre-HAART era. Those at greatest risk of infection are individuals with a CD4 count < 100 cells/μL [66]. It predominantly infects the small bowel mucosa, but in the immunocompromised patient, the large bowel and extraintestinal sites may be involved. The most common species infecting humans in the UK are *C. hominis* and the zoonotic species *C. parvum* and *C. meleagridis* [67]. In areas with a low rate of environmental contamination and where HAART is widely available, cryptosporidiosis has an incidence of < 1 per 100 person-years among HIV-seropositive individuals. Ingestion of cryptosporidium oocysts leads to transmission of the parasite. Faeces from infected animals, including humans, can contaminate the water supply with viable oocysts, which are highly resistant to chlorination. Transmission may also occur during sex, particularly via the faecal–oral route [68].

4.4.3.2 Presentation. Cryptosporidiosis should be considered in any individual with an acute or subacute history of profuse, non-bloody watery diarrhoea. In immunocompetent individuals, cryptosporidiosis presents as an acute, self-limiting diarrhoeal illness, which may be accompanied by nausea, abdominal cramps and low-grade pyrexia, lasting up to 14 days. In HIV-seropositive individuals with a CD4 count < 50 cells/μL there is a worsening of these symptoms, and stool volumes of up to 24 litres per day have been described, although more commonly, 2–3 litres per day are passed [69]. Malabsorption may be present.

As the epithelium of both the pancreatic duct and biliary tract can be infected, cholangitis and pancreatitis may occur in individuals with prolonged infection [70]. Sclerosing cholangitis presents with right upper quadrant pain, vomiting and raised alkaline phosphatase levels.

4.4.3.3 Diagnosis. The diagnosis of cryptosporidiosis is made by a stool flotation method with subsequent Ziehl–Neelsen, auramine phenol or acid-fast trichrome staining to differentiate oocysts from yeasts [71]. Oocysts may be detected more easily by direct immunofluorescence or enzyme-linked immunosorbent assay [72], which have a similar sensitivity to PCR techniques [73]. In individuals with profuse diarrhoea, cryptosporidiosis may be detected in a single stool sample, but multiple samples may be required in those with less severe infection as oocyst excretion may be intermittent.

Small bowel and rectal histology may be useful although the latter has a low sensitivity for diagnosis. In individuals with abdominal pain, endoscopic retrograde cholangio-pancreatography (ERCP) may reveal ampullary stenosis and sclerosing cholangitis with associated thickening of the gall bladder wall.

4.4.3.4 Treatment. There is no specific treatment targeting cryptosporidium directly. Early HAART is imperative and is associated with complete resolution of infection following restoration of immune function [74,75]. In individuals with profuse diarrhoea, therapeutic drug monitoring may be required to confirm adequate absorption of antiretroviral agents.

Paromomycin is active in animal models [76], although a recent meta-analysis has shown no evidence for clinical effectiveness [77]. A study combining paromomycin with azithromycin reported substantial reduction in stool frequency and volume, together with diminished oocyst shedding [78]. Paromomycin was given orally as 500 mg four times daily or 1 g twice daily for up to 12 weeks. The dose of azithryomycin was 500 mg daily. However the small numbers in this study and the limited experience of this combination preclude its choice as a front line therapy. Nitazoxanide has been approved for use in immunocompetent individuals but has not been shown to be superior to placebo in the severely immunocompromised [79]. If used, nitazoxanide is given at a dose of 500 mg twice daily for 3 days, but may be required for up to 12 weeks. Trials have also investigated a larger dose of 1 g bd po [80]. When an anti-cryptosporidial agent is chosen nitazoxanide is the preferred agent but its efficacy is limited in more immunocompromised patients.

Supportive therapy with iv fluid replacement/antimotility agents is essential.

- First-line treatment for cryptosporidiosis is with effective antiretroviral therapy (category recommendation III).

- Nitazoxanide is effective in adults and children who are not severely immunosuppressed (category IIb recommendation).

4.4.3.5 Impact of HAART. The use of optimized HAART should be continued to prevent relapse

4.4.3.6 Prevention. Standard drinking water chlorination techniques are not sufficient to eradicate the parasite. Specific filtration employing an 'absolute' 1-micron filter is required [81]. Bottled water is not necessarily a safer option. Boiling of water should be advocated.

4.4.4 Microsporidiosis

4.4.4.1 Background and epidemiology. Microsporidiosis, due to obligate intracellular parasites related to fungi, occurs in severely immunocompromised individuals, most commonly in those with a CD4 count < 100 cells/μL [82,83]. Some species cause gastrointestinal disturbance, such as diarrhoea and cholangitis, and other genera are associated with upper respiratory and ophthalmic infections.

The microsporidia most commonly linked to gastrointestinal illness are *Enterocytozoon bieneusi* and *Encephalitozoon* (formerly *Septata*) *intestinalis*. Gut infection is acquired by swallowing cysts, usually in water [82]. Pre-HAART studies showed variability in the prevalence of microsporidiosis (2–70%) in the immunosuppressed HIV population with diarrhoea [82,83]. The incidence has decreased with the introduction of HAART.

4.4.4.2 Presentation. Watery, non-bloody diarrhoea, with associated malabsorption, is the commonest presentation of gastrointestinal infection. Sclerosing cholangitis may occur. Encephalitis, sinusitis, myositis, renal, ocular and disseminated infection have also been described.

4.4.4.3 Diagnosis. Examination of three stools with chromotrope and chemofluorescent stains is often sufficient for diagnosis. If stool samples are consistently negative, a small bowel biopsy should be performed [84]. Stains such as Giemsa, acid-fast or haematoxylin and eosin can be used to visualize microsporidia in biopsy specimens [85]. In disseminated infections due to *Encephalitozoon* spp, organisms may also be found in the deposit of spun urine samples.

Electron microscopy remains the gold standard for confirmation and speciation [86]. PCR may be used to identify to species level.

4.4.4.4 Treatment. There is no specific treatment for microsporidial infection. Early HAART is imperative and associated with complete resolution of gastrointestinal symptoms following restoration of immune function [74,87]. Therapeutic drug monitoring may be required to confirm adequate absorption of antiretroviral agents. Thalidomide may be effective for symptom control in some individuals [88].

E. bieneusi may respond to oral fumagillin (20 mg three times daily for 14 days) [89], but with significant haematological toxicity [91]. This agent is not currently widely available. Nitazoxanide, albendazole and itraconazole have also been studied. Of these agents, albendazole (400 mg twice daily for 21 days) is recommended for initial therapy, particularly for *E. intestinalis* (category III recommendation) [91,92].

4.4.4.5 Impact of HAART. Optimized HAART should be used to maintain CD4 cell counts and prevent relapse.

4.4.4.6 Prevention. As for Cryptosporidium.

4.4.5 Other parasites and helminths causing diarrhoea (usually chronic)

4.4.5.1 Background. Faecal carriage and clinical illness due to parasites such as *Giardia lamblia* (*intestinalis*) and *Entamoeba histolytica/dispar* were described in homosexual men before the HIV epidemic, reflecting increased risk behaviour [93–95], see Table 4.3.

4.4.5.2 Giardiasis. Giardiasis usually presents with chronic diarrhoea with constitutional symptoms. GI symptoms include nausea, bloating, crampy abdominal pain, indigestion and belching. Prolonged diarrhoea may result in a malabsorptive state. Giardiasis is treated with metronidazole 400 mg tid po for 7 days or 1 g daily for 3 days, or tinidazole 500 mg bd po for 7 days or 2 g once only po (category III recommendation) [96], see Table 4.3. Alternatives include albendazole, paromomycin or nitazoxanide [79,97–100].

4.4.5.3 Amoebiasis. Entamoeba histolytica is a protozoan that causes intestinal infection including colitis and extra-intestinal invasive disease, most commonly liver abscesses. Entamoeba infection is most commonly seen in men who have sex with men [101]. Fever, abdominal pain and either watery or bloody diarrhoea are the most frequent symptoms and amoebic colitis occurs at a range of CD4 counts and is not limited to individuals with CD4 T-cell counts < 200 cells/μL [102]. Hepatic abscesses are the commonest extra-intestinal manifestation. Diagnosis involves microscopy of at least three stool samples for the detection of trophozoites or cysts. Antigen detection or PCR of stool may also be performed and endoscopy with biopsy can aid diagnosis if stool analysis fails to confirm the diagnosis or diagnostic uncertainty remains. Serology can be employed but remains positive for years after exposure and therefore direct identification of entamoeba is desirable. Extra-intestinal lesions are diagnosed in the appropriate clinical setting by imaging combined with serology. Treatment is most often with metronidazole 800 mg tid po for 10 days although tinidazole 2 g once a day po for three days may be used as an alternative. These agents are followed by diloxanide fuorate 500 mg tid po or

Table 4.3 Treatment for selected parasites in association with HIV

Parasite	Diagnosis	Treatment	Impact of HAART
Cyclospora cayetanensis	ZN or auramine staining of faeces. Oocysts can also be seen using phase contrast microscopy, and PCR-based diagnostic methods have been developed	TMP-SMX 960 mg bd for 7 days Alternatives include ciprofloxacin 500 mg bd but response slower and incomplete	Antibiotic prophylaxis required until effective response to ART [91,92]
Entamoeba histolytica	Faecal microscopy with or without faecal antigen/PCR or colonic biopsy. Serology and imaging for extraintestinal disease	Metronidazole 800 mg tid for 10 days or tinidazole 2 g once a day for 3 days followed by either diloxanide fuorate 500 mg tid po for 10 days or paromomycin 30 mg/kg/day in three divided doses po for 10 days	Nil
Giardia lamblia	Faecal microscopy or faecal antigen detection ELISA. Rarely, duodenal biopsy or duodenal fluid sample for microscopy	Metronidazole 400 mg tid for 7 days or 1 g daily po for 3 days Alternative is tinidazole 2 g po once only or 500 mg bd for 7 days	Nil
Isospora belli	Direct microscopy of iodine-stained faecal smears or fluorescence microscopy, but most laboratories rely on faecal stains including ZN, auramine or safranin-methylene blue	TMP-SMX 960 mg bd for 7 days Alternatives include TMP-SMX 960 mg qid for 10 days or ciprofloxacin 500 mg bd but response is slower and incomplete with ciprofloxacin	Antibiotic prophylaxis required until effective response to ART
Strongyloides stercoralis	Stool culture to detect larvae in faeces. It may be found in duodenal biopsies or by string test	Preferred choice is oral ivermectin (200 μg/kg once or twice only). Alternatives include albendazole 400 mg bd for 3 days	

ZN, Ziehl–Neelsen.

paromomycin 30 mg/kg/day in three divided doses po, both administered for 10 days, to eradicate luminal infection. Good responses to metronidazole-based therapy are described for HIV-seropositive individuals [102].

4.4.5.4 Cyclospora Cayetanensis. Cyclospora cayetanensis, a coccidian parasite of the small bowel, is widespread throughout the tropics and has caused large outbreaks of food-borne illness in the USA in imported foods. It causes prolonged watery diarrhoea that may last for months in patients with HIV, in whom biliary involvement has also been reported [103,104].

The diagnosis involves the microscopic detection of oocysts but fluorescence microscopy and real-time PCR may be used, where available [104]. The clinical and parasitological response to standard doses of TMP-SMX (960 mg twice daily) is rapid and 7 days is usually sufficient [105]. Ciprofloxacin 500 mg twice daily is an alternative but response is slower and incomplete (category IIb) [105]. Relapses are described in over 40% of HIV-seropositive patients and secondary prophylaxis with TMP-SMX (960 mg three times a week) or ciprofloxacin (500 mg three times a week) is needed in the absence of effective ART [103,105].

4.4.5.5 Isospora belli. Isospora belli has no known animal host but is widespread geographically, causing self-limiting small bowel diarrhoea in HIV-seronegative individuals. It is implicated in 10–20% of cases of chronic HIV-related diarrhoea in the tropics and is an occasional cause of biliary disease. Treatment traditionally has been with TMP-SMX 960 mg qid po for 10 days though 960 mg bd appears also to be effective (category III recommendation) [105,106] and secondary prophylaxis with the same antibiotic (960 mg three times a week) is essential as relapse is common and there is indirect [107] and direct evidence for efficacy [105,106]. Ciprofloxacin is a less effective alternative for both treatment and prophylaxis [105]. Anecdotal reports suggest possible roles for pyrimethamine 75 mg/day for treatment and 25 mg/day for secondary prophylaxis in patients who are allergic to sulphonamides [108].

4.4.5.6 Strongyloides stercoralis. Strongyloides stercoralis is a gut nematode that causes chronic gastrointestinal and skin problems due to its autoinfective life-cycle, and can disseminate to cause life-threatening hyperinfection syndromes in the immunosuppressed [99, 109–111]. Despite anecdotal reports, there is no conclusive evidence that infection or hyperinfection is more common in patients with HIV, although it may be implicated in immune reconstitution syndromes [112]. Corticosteroid use remains a major factor in case reports of hyperinfection syndrome of HIV-seropositive individuals [113]. Eosinophilia is present in most but not all patients. Uncomplicated infection is treated with ivermectin 200 μg/kg once a day po for 1 or 2 days, which is more effective than the alternative treatment of albendazole 400 mg bd po for 3 days [114–116] (category III recommendation). Case reports in HIV-seropositive individuals highlight the importance of following stool specimens and repeating treatment when

parasites are apparent again. Some physicians repeat the initial 2 days of ivermectin treatment after 2 weeks [117]. Hyperinfection is treated with 14 days' therapy or longer until larvae clear. The basis of these recommendations, however, is largely from studies in non-HIV-related cases, although case reports of treatment in HIV exist [98]. Serology and stool examination should be checked at intervals over the first 2 years after treatment as autoinfective migrating larvae may not be eradicated by initial treatment.

4.5 References

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