4. Gastrointestinal opportunistic infections

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4.1 Methods

The PubMed database was searched using the terms shown in Appendix 1. PICO questions were set (see Appendix 1) and the literature reviewed to address each question. Evidence was assessed and graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (see Appendix 2).

4.2 General overview

Gastrointestinal (GI) symptoms occur frequently in people living with HIV (PLWH). Dysphagia and diarrhoea (Table 4.1) may be caused by a wide variety of infections. 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 incidence of opportunistic infections has fallen as most PLWH take combination antiretroviral therapy (cART), however there remain some differences in type of pathology seen compared to non-HIV-infected populations [1]. If a cause of persisting GI symptoms is not apparent, consultation with a gastroenterologist is indicated because PLWH are also susceptible to many of the same conditions as the non-HIV-infected population. Co-infection with hepatitis B or C virus is not discussed in these guidelines as it is the subject of separate guidelines [2].

4.3 Oropharyngeal infections and oesophagitis

4.3.1 Candidiasis

The organisms that most commonly cause oropharyngeal infections and oesophagitis are *Candida* spp. Persistent or recurrent oesophageal candidiasis has decreased in the combination antiretroviral therapy (cART) era and most often indicates poor HIV viral control [3]. Candidiasis of the upper GI tract is discussed in detail in Chapter 7.

4.3.2 Other causes of oesophagitis and oropharyngeal infections

Oesophagitis should be suspected in patients who experience pain on swallowing, with or without symptoms of reflux or dysphagia. The other major HIV-related infectious causes of oesophagitis include herpes simplex virus (HSV) and cytomegalovirus (CMV) infections,

which cause ulceration and may coexist with candidiasis, especially in PLWH with CD4 counts <100 cells/mm^3. Tuberculosis is a rare cause of oesophageal or oropharyngeal disease. Idiopathic ulcers are also common. Other non-infectious causes of dysphagia 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 that are likely to be encountered in PLWH [4].

4.3.3 Diagnosis

- *Oral and oesophageal candidiasis are clinical diagnoses (Grade 1B, moderate-quality evidence).*
- *Microbiological confirmation and susceptibility testing of* **Candida** *spp. is required when symptoms of candidiasis persist or recur during antifungal therapy (Grade 1B, moderate-quality evidence).*
- *Endoscopic diagnosis by swab and/or biopsy should be undertaken in patients with oesophageal symptoms without oropharyngeal candidiasis and in patients who do not respond to initial treatment or who relapse (Grade 1C, low-quality evidence).*

A randomised trial demonstrated that initial empirical therapy for candidiasis is a reasonable first approach in uncomplicated oesophagitis [5]. Endoscopy should be performed if symptoms have failed to resolve after an empirical trial of azoles, with appropriate swab and/or biopsy if abnormalities are seen. Adequate and appropriate specimens must be collected to enable histological and virological diagnoses, together with cultures and anti-fungal susceptibility testing for the identification of azole-resistant *Candida* strains. For mouth ulcers, HSV polymerase chain reaction (PCR) or culture tests should be used for diagnosis.

4.3.4 Treatment

- *Fluconazole remains the preferred treatment option for oropharyngeal or oesophageal candidiasis on the basis of an updated Cochrane database systematic review (Grade 1A, high quality of evidence).*
- *CMV oesophagitis should be treated with intravenous (iv) ganciclovir 5 mg/kg twice daily (bd) for 2–4 weeks, or until symptoms/signs have resolved (Grade IB) [6,7]; oral valganciclovir (900 mg bd) may be substituted for iv ganciclovir for some or all of the duration if symptoms are not severe enough to interfere with swallowing and oral absorption (Grade IC).*
- *Ongoing maintenance therapy for CMV oesophagitis is not routinely indicated, unless there is concomitant ophthalmological disease (Grade IC).*
- *HSV oesophagitis should be treated with aciclovir 5–10 mg/kg three times daily (tid) iv, followed by oral (po) valaciclovir 1 g bd or famciclovir 500 mg tds for a total of 14 days or until healing is complete (Grade 1B).*

Further discussion of treatment of candidiasis can be found in the BHIVA Opportunistic Infection Guidelines, Chapter 7. Foscarnet 90 mg/kg bd iv may be used in cases of

ganciclovir-resistant CMV or 40 mg/kg bd or tid for aciclovir-resistant HSV [8]. Systemic cidofovir 5 mg/kg once weekly for 2 weeks is an alternative treatment for CMV or HSV where there is intolerance of or resistance to other drugs.

4.4.2.5 Prevention and impact of cART

- **cART is the mainstay of prevention of upper GI tract infections with candida or herpesviruses (*Grade* 1B).**

4.4 Diarrhoea

4.4.1 Epidemiology of acute diarrhoea

Diarrhoea is common among PLWH, even in the era of cART. A meta-analysis of post-2008 clinical trials demonstrated that the prevalence of diarrhoea was 18% among PLWH on treatment [9]. Diarrhoea is normally defined as having more than two bowel movements per day, with acute diarrhoea occurring for less than 4 weeks and chronic diarrhoea for more than 4 weeks. Chronic diarrhoea may be more associated with opportunistic infections in PLWH than in the general population, particularly those with lower CD4 counts.

Table 4.1 Major causes of HIV-related diarrhoea

Bacteria	Parasites and fungi	Viruses	Non-infectious causes
Campylobacter spp.	*Cryptosporidium* spp.	Cytomegalovirus	ART
Clostridioides difficile	*Cyclospora cayetanesis*	Herpes simplex virus	Kaposi's sarcoma
Escherichia coli (pathotypes)	*Giardia lamblia*	Rotavirus	Lymphoma
Salmonella spp.	*Entamoeba histolytica*	Norovirus	Pancreatic exocrine insufficiency
Shigella spp.	*Isospora belli*	Adenovirus	
Mycobacterium tuberculosis	*Microsporidia*	Astrovirus	
Mycobacterium avium-intracellulare complex	*Strongyloides stercoralis*	Coronavirus	
Mycobacterium kansaii			
Chlamydia trachomatis/ Lymphogranuloma verereum			

4.4.2 Bacterial gastroenteritis

4.4.2.1 Aetiology

A range of bacteria commonly cause gastroenteritis in PLWH (Table 4.2). *Clostridioides difficile* was the most common cause of diarrhoea among PLWH in a US cohort study [10]. However, this has not been replicated in other studies in the developed world. *C. difficile* is prevalent in high-income and low/middle-income countries (LMICs) [11-13] and spans the pre- and post-cART eras [14]. Invasive non-typhoidal salmonellosis (iNTS) was recognised early in the HIV epidemic to be strongly associated with immunosuppression in high-income countries [15-17] and LMICs [18-20]. As in HIV-negative individuals, other bacterial pathogens causing diarrhoea include *Escherichia coli, Campylobacter* spp. and *Shigella* spp [21-23].

Prevalence of *Shigella* spp. was higher among HIV-positive men who have sex with men (MSM) compared to HIV-negative MSM in the UK [24] and other pathogens such as *Campylobacter* spp. are increasingly identified among HIV-positive MSM [25]. Lymphogranuloma venereum (LGV), caused by *Chlamydia trachomatis*, can be associated with diarrhoea as part of proctocolitis or enteritis syndromes and is increasingly common in MSM in Europe [26,27].

4.4.2.2 Risk factors

Older age and lower CD4 count increase the likelihood of diarrhoea in PLWH [28]. Residence or travel to LMICs increases the risk of diarrhoea due to greater pathogen exposure. In addition, MSM are at risk of sexually acquired diarrhoeal disease. Hospitalisation, gastric acid suppression, lower CD4 count and antibiotic use are risk factors for *C. difficile* infection in PLWH [11,14].

4.4.2.3 Presentation and diagnosis

- ***Stool and blood cultures should be included in the routine diagnostic work-up of diarrhoea in PLWH (Grade 1D, very low-quality evidence).***
- ***C. difficile toxin assessment and/or culture should be carried out in all PLWH presenting with acute diarrhoea (Grade 1D).***

The spectrum of clinical presentation ranges from asymptomatic infection to severe dehydration and death. Bacterial gastroenteritis may cause bloody diarrhoea and abdominal pain. Bacteraemia is more likely in PLWH, but remains uncommon overall [29,30]. In PLWH, iNTS infections present with febrile illness or sepsis syndromes, and diarrhoea may be absent or a less prominent feature [20]. Presenting symptoms of *C. difficile* infection in PLWH are similar to those in HIV-negative individuals [31,32]. Case series suggest that *C. difficile* infection is no more severe in PLWH [33,34]. Recent outbreaks of LGV were associated more with anorectal symptoms than with inguinal lymphadenopathy or ulceration; these symptoms may include tenesmus, constipation, diarrhoea and anal discharge [24].

Table 4.2 Diagnosis and treatment of selected bacterial infections

Bacteria	Association with HIV	Diagnosis	Treatment	Impact of cART
Campylobacter spp.	Indeterminate/yes with MSM	Stool culture (preferred), PCR	If CD4 $\geq$200 cells/mm^3, usually no treatment required; if CD4 <200 cells/mm^3, treat as per local guidelines	May reduce likelihood of future infection
Clostridioides difficile	Yes	PCR/NAAT, EIA-GDH, EIA for toxins A + B, toxigenic culture, colonoscopy + biopsy, CT scan	As per national guidelines: metronidazole if non-severe. Vancomycin or fidaxomicin if severe or recurrent. Consider faecal transplant in recurrent cases	Reduces likelihood of future infection
Escherichia coli	Indeterminate/yes	Stool culture (preferred), EIA for Shiga toxin	If CD4 $\geq$200 cells/mm^3, usually no treatment required; if CD4 <200 cells/mm^3, treat as per local guidelines	May reduce likelihood of future infection
Salmonella spp.	Indeterminate/yes	Stool culture (preferred), PCR	If CD4 $\geq$200 cells/mm^3, usually no treatment required; if CD4 <200 cells/mm^3, treat as per local guidelines	May reduce likelihood of future infection
Shigella spp.	Indeterminate/yes with MSM	Stool culture (preferred), PCR	If CD4 $\geq$200 cells/mm^3, usually no treatment required; if CD4 <200 cells/mm^3, treat as per local guidelines	May reduce likelihood of future infection
Mycobacterium tuberculosis	Indeterminate/yes	Colonoscopy + biopsy for histology (AFB smear) + mycobacterium culture (preferred to PCR for intestinal tuberculosis); intestinal tissue PCR, CT preferred mode of imaging	See BHVIA guidelines on management of tuberculosis in adults living with HIV 2018	May reduce likelihood of future infection
Mycobacterium avium-intracellulare complex	Indeterminate	Definitive diagnosis requires culture in blood or from bone marrow aspirate or fluid from a normally sterile site or biopsy specimen	See Chapter 8: Mycobacterium avium-intracellulare complex	May reduce likelihood of future infection
Mycobacterium kansaii	Indeterminate	Colonoscopy + biopsy for histology (AFB smear) + mycobacterium culture (preferred to PCR for intestinal tuberculosis); intestinal tissue PCR, CT preferred mode of imaging	See Chapter 8: Mycobacterium kansaii	May reduce likelihood of future infection
Chlamydia trachomatis/LGV	Yes with MSM	Rectal swab NAAT, if *C. trachomatis* positive then test DNA for LGV-specific serovars	As per national guidelines: oral doxycycline 100 mg bd for 21 days	No evidence of biological effect, possible effect of serosorting

AFB, acid-fast bacilli; CT, computed tomography; EIA, enzyme immunoassay; EIA-GDH, EIA for *C. difficile* glutamate dehydrogenase; NAAT, nucleic acid amplification test.

4.4.2.4 Treatment

- ***Acute bacterial diarrhoea in HIV-seropositive individuals with CD4 counts >200 cells/mm³ usually does not require treatment, but should be treated when the CD4 count is <200 cells/mm³ (Grade 2D, very low-quality evidence).***
- ***Acute bacterial diarrhoea should be treated as per sensitivity tests and local guidance (Grade 2D).***
- ***C. difficile** **infection should be treated as per national guidelines: metronidazole if non-severe, with vancomycin or fidaxomicin if severe or recurrent; consider faecal transplant in recurrent cases (Grade 1A).***

If a bacterial cause is suspected from the history, antimicrobial therapy may be indicated. Principles of therapy are as for HIV-negative individuals. We suggest that acute bacterial diarrhoea in individuals with preserved CD4 counts (>200 cells/mm³) does not usually require treatment. In general, when individuals present with acute bacterial diarrhoea and a CD4 count <200 cells/mm³, therapy will be indicated. When indicated, the choice should be guided by sensitivity testing. In cases where the patient presents with signs of sepsis or severe symptoms, the benefits of empirical treatment may outweigh the potential risks and empirical treatment should be commenced. There have been increasing numbers of reports of ciprofloxacin resistance in *Campylobacter* spp., *Shigella* spp. and *Salmonella* spp. [35-37] and choice of empirical agent should be consistent with local guidance.

For treatment of *C. difficile* diarrhoea, as with the management of HIV-negative cases, the first step is to stop the aetiological antibiotic where possible and isolate the patient. Principles of therapy for *C. difficile* infection are as for HIV-negative individuals and therapy is indicated regardless of the CD4 count. *C. difficile* infection should be treated according to Public Health England guidelines [38]; for non-severe *C. difficile* infection metronidazole is indicated, and severe infection should be treated with vancomycin or fidaxomicin should be considered [38,39]. There is no evidence for the use of probiotics for *C. difficile* treatment [40]. The treatment response for HIV-positive and HIV-negative people appears similar and complications do not appear to be more or less common in PLWH. For recurrent *C. difficile* infection, treat with fidaxomicin or vancomycin [38]; faecal transplant may be considered and can be effective in the general population [41-43]. Based on data from case reports and case series, donor stool transplant appears to be safe and effective in PLWH, including those with a low CD4 count [42].

A Cochrane review on antibiotic treatment for *C. difficile* in the general population demonstrated that vancomycin was more effective than metronidazole for achieving symptomatic cure, but the quality of the evidence was very low [39]. The review also found moderate-quality evidence that fidaxomicin was more effective than vancomycin at achieving symptomatic cure, however only two papers were included in this analysis and both were non-inferiority trials and neither reported intention-to-treat data. Therefore, there is insufficient evidence to change the current recommendations.

4.4.2.5 Prevention and impact of cART

- **cART is the mainstay of preventing bacterial diarrhoea (*Grade* 1B).**

Trimethoprim-sulphamethoxazole (co-trimoxazole) reduced the incidence of infectious diarrhoea in the pre-cART era [44]. The introduction of cART has been more effective than antimicrobial prophylaxis in preventing recurrence of non-typhoidal salmonella [45,46]. If given, the duration of antimicrobial prophylaxis, with agents such as fluoroquinolones, need not exceed 30 days in patients established on cART [47].

The incidence of bacterial diarrhoea has declined steadily since the introduction of cART, therefore cART is the mainstay of preventing bacterial diarrhoea [48,49].

4.4.3 CMV and viral gastroenteritis

4.4.3.1 Background

A variety of viruses can cause gastroenteritis in PLWH (Table 4.3), of which CMV is the most important pathogen. CMV is a member of the herpes family of viruses. Primary CMV infection can occur at any stage throughout life, and the virus then remains dormant unless reactivated in the immunocompromised host. Globally, the seroprevalence of CMV varies widely between different risk groups and countries, but there is evidence of past CMV exposure in the majority of PLWH, especially among MSM. CMV is still the most common opportunistic pathogen causing viral enteritis in PLWH although the incidence has decreased substantially in the cART era [50]. Most cases of CMV disease occur in people with prior CMV infection and a CD4 cell count of less than 50 cells/mm^3 [51].

HIV-infected patients often present with non-specific GI symptoms. Although it can affect the entire GI tract, CMV infection frequently involves the oesophagus or the colon [52,53]. The most common complications of CMV colitis are weight loss, anorexia, abdominal pain, chronic unremitting diarrhoea and fatigue. There may also be systemic features of CMV infection such as fevers and cytopaenias. Toxic dilatation, haemorrhage and perforation are recognised serious complications.

In terms of the impact of cART, all patients with CMV of the GI tract should be assessed for retinitis and if present treatment should be initiated. If initial examination is negative, direct fundoscopy and ophthalmology review should be repeated if any visual symptoms occur. cART initiation is typically delayed by 2 weeks if CMV retinitis is also present to prevent the low but possible risk of immune reconstitution uveitis [54,55]. A delay of more than 2 weeks before starting cART after CMV colitis treatment has begun is not recommended. The presence of CMV-associated GI disease alone is not an indication to delay cART. Therapeutic drug monitoring to ensure adequate cART absorption is advised if the patient's HIV viral load does not become undetectable within a reasonable expected time frame.

Table 4.3 Diagnosis and treatment for selected viral infections

Virus	Association with HIV	Diagnosis	Treatment	Impact of cART
Cytomegalovirus	Yes	CMV PCR (preferred method), gastroscopy + colonoscopy biopsies + histology (if GI symptoms), CMV-specific T cell assays, CMV pp65 antigenaemia	Ganciclovir (5 mg/kg bd iv) 2–4 weeks/until symptoms resolution. For non-severe infection, oral valganciclovir (900 mg bd) may be used. Second line: iv foscarnet (90 mg/kg bd) for 2 weeks	Reduces likelihood of future infection
Herpes simplex virus	Indeterminate	Rectal swab NAAT or PCR for HSV	As per national guidelines: aciclovir 400 mg tds or valaciclovir 500 mg bd	May reduce likelihood of recurrence
Rotavirus	No/indeterminate	ELISA, latex agglutination testing, PCR (preferred method)	Supportive measures	May reduce likelihood of future infection
Norovirus	No	RT-PCR (preferred method), ELISA	Supportive measures	Nil
Adenovirus	Indeterminate	PCR, EIA, viral culture, histology, serology (use of multiple methods for diagnosis of adenovirus in immunocompromised host)	Cidofovir iv if clinically significant infection (rare) – induction: 5 mg/kg weekly for 2 weeks, maintenance: 5 mg/kg fortnightly	May reduce likelihood of future infection
Astrovirus	No/indeterminate	PCR (RT-qPCR preferred), EIA	Supportive measures	May reduce likelihood of future infection
Coronavirus	No/indeterminate	RT-PCR (preferred), EIA	Supportive measures	May reduce likelihood of future infection

ELISA, enzyme-linked immunosorbent assay; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative RT-PCR.

4.4.3.2 Diagnosis

- ***CMV colitis should be diagnosed by biopsy with characteristic features seen on histopathology (Grade IC).***

The diagnosis of CMV-associated gastrointestinal disease is based on the clinical symptoms of GI disease, characteristic mucosal ulceration seen on endoscopy and intracellular and intracytoplasmic 'owl's eye' inclusions seen on pathology, with positive immunohistochemical staining for CMV. CMV viraemia as detected by PCR, antigen assays or culture is non-specific for the presence of colitis in patients with a low CD4 count [56-58].

With respect to serological tests CMV antibody is not useful in diagnosing CMV enteritis in PLWH, however this diagnosis is unlikely if the patient is CMV IgG seronegative.

4.4.3.3 Primary prophylaxis

- ***The use of prophylactic oral ganciclovir or valganciclovir in PLWH with low CD4 counts is not advised due to lack of proven benefit and associated possible toxicity (Grade 1B).***

Opportunistic infection of the GI tract with CMV in PLWH is best prevented by maintaining the CD4 count >100 cells/mm³ with cART.

4.4.3.4 Initial treatment

- ***CMV colitis should be treated with ganciclovir (5 mg/kg bd iv) for 2–4 weeks or until symptoms have resolved (Grade 1B).***
- ***Oral valganciclovir (900 mg bd) may be used for non-severe CMV colitis or when the patient is able to tolerate and absorb oral medication (Grade 1C).***
- ***Foscarnet (90 mg/kg bd iv) for 2 weeks is a second-line alternative in cases of ganciclovir-related toxicity or ganciclovir resistance (Grade 1B).***

Ganciclovir is the preferred treatment for induction therapy for CMV colitis [59]. Foscarnet is also effective but ganciclovir is the preferred agent because of fewer side effects [60]. Systemic cidofovir 5 mg/kg once weekly for 2 weeks is an alternative treatment for CMV where there is intolerance to other antiviral therapies.

Oral valganciclovir may be used for induction therapy in patients who can tolerate and absorb oral medication and where there is evidence of mild or resolving infection. However the evidence base for this is predominantly from treatment of CMV retinitis [61].

4.4.3.5 Maintenance therapy

- ***Maintenance therapy, usually with oral valganciclovir 900 mg od, should be given to patients with concurrent CMV retinitis and to the minority of those who relapse after induction therapy [62] (Grade 2B).***
- ***Prophylactic antiviral therapy can be stopped once there is evidence of significant immune reconstitution, when the patient is on cART and has a CD4 count consistently above 100 cells/mm³ for more than 6 months (Grade 1C).***

Chronic maintenance therapy following treatment of acute CMV disease is not recommended unless clinical relapse occurs.

4.4.3.6 Treatment failure

- ***Ganciclovir resistance, confirmed via identification of mutations in the UL97 gene, should be treated with foscarnet 90 mg/kg bd (Grade 2B).***

Failure of therapy for CMV-related GI disease may be due to lack of immune reconstitution, inadequate anti-viral levels as a result of poor absorption or antiviral medication resistance. Alternative diagnosis or concurrent GI infection should also be considered. Antiviral-resistant, HIV-related CMV colitis is rare. Prolonged CMV treatment (>6 weeks) and very high initial CMV viral load in blood (>10^6 IU/mL) are risk factors for resistance.

In cases of relapsed CMV retinitis, treatment options include ganciclovir plus foscarnet [63] but there are limited data on this combination in treating relapsed CMV-associated colitis and the treatment is associated with considerable toxicity.

CMV resistance to ganciclovir can be confirmed by detection of mutations in the *UL97* gene sequence [64]. Resistance to foscarnet or cidofovir occurs through mutations in the CMV *UL54* gene. High-level resistance to ganciclovir is associated with resistance to cidofovir (and occasionally foscarnet) [65-67]. These genotypic assays can be completed in a few days. Phenotypic resistance testing is not routinely available. There are anecdotal reports supporting the use of other agents, such as cidofovir, in GI antiviral-resistant CMV disease as well as high-dose ganciclovir or high-dose valganciclovir [68]. Novel anti-CMV therapies are becoming available including, brincidofovir, maribavir and letermovir, and may be obtained on a named-patient basis.

Monitoring of ganciclovir/valganciclovir levels is not routinely recommended but should be considered in cases of inadequate response where there is concern about inadequate oral absorption, or where dose adjustment has been made due to renal impairment.

Awareness of drug interactions between cART agents and anti-CMV drugs is important. Risk factors for these interactions would include advanced age, certain comorbidities and concomitant nephrotoxic medications [69]. Reports of renal toxicity associated with concurrent use of ganciclovir/valganclovir and tenofovir have been published [70].

4.4.3.7 Other viral infections

HSV, adenovirus, norovirus, astrovirus and rotavirus have also been implicated in the causation of viral enteritis in PLWH and there is some suggestion of increased severity in this population [71-74]. Only HSV has established treatment options and more commonly affects the oesophagus (see HSV oesophagitis above). Cidofovir shows activity against adenovirus although cases of clinically significant colitis caused by this virus are rarely reported [75]. There have been reports implicating coronavirus, which may coexist with bacterial pathogens [76] in acute diarrhoea, and adenovirus, which may coexist with CMV in patients with chronic diarrhoea [77]. HSVs (HSV-1 and HSV-2) can cause diarrhoea due to proctocolitis. Older age, lower CD4 count and travel to LMICs increase the risk of diarrhoea among PLWH. MSM and others who have anal sex are at risk of sexually acquired diarrhoeal disease [24].

The spectrum of clinical presentation 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. Supportive measures are the mainstay for viral gastroenteritis, primarily ensuring adequate hydration through oral or iv fluids. Treatment of CMV- and HSV-related disease is discussed in depth in other chapters.

The incidence of viral opportunistic infections has declined following the introduction of cART [49], and cART is the mainstay of preventing viral diarrhoea.

4.4.4 Parasitic and helminth infections

4.4.4.1 Background
A number of parasites and helminths can cause GI pathology in PLWH (Table 4.4), and diagnosis and treatment are summarised below

Table 4.4 Diagnosis and treatment for selected parasitic infections

Parasite	Association with HIV	Diagnosis	Treatment	Impact of cART
Cryptosporidia spp.	Yes	Faecal microscopy and PCR. Small bowel or rectal biopsy can be considered	Effective cART. Nitazoxanide 500 mg bd for 3 days (extended up to 12 weeks) may be considered	Effective cART essential for treatment and to prevent relapse
Microsporidia spp.	Yes	Faecal microscopy with chromotrope and chemofluorescent stains. PCR where available. Small bowel biopsy can be considered	Effective cART. Albendazole 400 mg bd for 14 days can be given in addition in *Encephalitozoon intestinalis* infection	Effective cART essential for treatment and to prevent relapse
Giardia lamblia	No/indeterminate	Faecal microscopy or faecal antigen-detection ELISA. Rarely duodenal biopsy or fluid sample for microscopy	Metronidazole 400 mg tds po for 7 days or 1 g daily for 3 days. Alternative: tinidazole 500 mg bd po for 7 days or 2 g once only	Nil
Entamoeba histolytica	No	Faecal microscopy and PCR. Serology and imaging for extra-intestinal disease	Metronidazole 800 mg tds po for 5–10 days (alternative: tinidazole 2 g od po for 3 days) followed by diloxanide furoate 500 mg tds po for 10 days	Nil
Cyclospora cayetanensis	Yes/indeterminate	Faecal microscopy with ZN or auramine staining and PCR	Co-trimoxazole 960 mg bd for 7 days followed by 960 mg 3 times weekly as prophylaxis	Antibiotic prophylaxis required until effective response to cART
Isospora belli	Yes	Faecal microscopy of iodine-stained smears	Co-trimoxazole 960 mg bd po for 7 days.	Antibiotic prophylaxis

		or ZN, auramine or safranin-methylene blue-stained smears	Alternative: co-trimoxazole 960 mg qds for 10 days or ciprofloxacin 500 mg bd followed by the same antibiotic as prophylaxis	required until effective response to cART
Strongyloides stercoralis	No/indeterminate	Stool culture to detect larvae in faeces, at duodenal biopsy or using the string test	Ivermectin 200 µg/kg od po for 1 or 2 days. Alternative: albendazole 400 mg bd po for 3 days	Nil
Schistosomiasis spp.	No/indeterminate	Stool or urine microscopy for ova. Serology in those without history of previous treatment	Praziquantel; dose determined by species	Nil

qds, four times daily; ZN, Ziehl-Neelsen.

4.4.4.2 *Cryptosporidium* spp.

Background and epidemiology

Cryptosporidium is a ubiquitous protozoan parasite, which can cause diarrhoeal disease in humans. Infection is spread by the ingestion of as few as 10–100 cryptosporidium oocysts following contamination of the water supply by the faeces of infected animals or humans [78]. Sexual transmission can also occur, particularly via the faecal–oral route [79]. *Cryptosporidium* is a significant cause of chronic diarrhoea in patients with advanced HIV, of diarrhoea in children and of zoonotic and waterborne outbreaks [80]. PLWH are at greatest risk when their CD4 count is <100 cells/mm^3 [81]. *Cryptosporidium* predominately infects the small bowel mucosa, but the large bowel and extraintestinal sites may be involved in the immunocompromised patient. Routine typing of isolates from cryptosporidiosis cases between 2000 and 2008 in England and Wales identified *C. hominis* in 51% of cases, *C. parvum* in 44%, mixed infection with *C. hominis* and *C. parvum* in 0.4% with the remainder either non-typable or other species [82].

Presentation

Cryptosporidiosis should be considered in any individual with an acute or subacute history of profuse, non-bloody, watery diarrhoea. Fever is present in approximately one-third of patients and malabsorption is common. Nausea, vomiting and lower abdominal pain may also occur. Cryptosporidiosis is usually self-limiting within 14 days in immunocompetent individuals. In HIV-seropositive individuals with a CD4 count <50 cells/mm^3, symptoms are more severe and stool volumes of up to 24 L/day have been described, although 2–3 L/day are more commonly passed [83].

As the epithelium of both the pancreatic duct and biliary tract can be infected, cholangitis and pancreatitis may occur in individuals with prolonged infection [84]. Sclerosing cholangitis presents with right upper quadrant pain, vomiting and raised alkaline phosphatase levels. Cases of pulmonary cryptosporidiosis in those with advanced HIV have also been reported [85,86] and raise the possibility of respiratory transmission of cryptosporidiosis [87].

Diagnosis

- *Where a diagnosis of cryptosporidiosis is suspected, microscopy of fresh, unconcentrated stool samples should be performed (**Grade** 1C).*
- *Repeat samples may be required due to intermittent oocyst secretion (**Grade** 1C).*
- *Where available PCR should be used in addition to stool microscopy to aid in the detection and speciation of cryptosporidiosis (**Grade** 1B).*

Cryptosporidiosis can be diagnosed by the detection of oocysts in fresh, unconcentrated stools by microscopy of smears stained with either auramine phenol or modified Ziehl-Neelsen. In cases of profuse diarrhoea, cryptosporidiosis may be detected in a single stool sample, but in mild disease repeat samples may be required due to intermittent oocyst excretion. Concentration methods are not required where stool samples are collected fresh without preservatives but may be helpful in very watery samples. Immunofluorescence microscopy can improve diagnostic sensitivity but requires additional resources and costs are increased [86].

Increasingly UK laboratories are using enzyme immunoassays that have a similar sensitivity and specificity to microscopy with auramine phenol [88,89]. PCR can be used for the detection and speciation of cryptosporidium with excellent sensitivity and specificity [90].

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

Treatment

- *Effective cART is the first-line treatment for cryptosporidiosis (**Grade** 1C).*
- *Nitazoxanide is effective in adults and children who are not severely immunosuppressed (**Grade** 2B).*

In advanced HIV, restoration of the immune system with effective cART is associated with full resolution of cryptosporidial infection [91,92]. Although a number of drugs have shown activity *in vitro*, in animal models and in immunocompetent patients, their use in HIV has been disappointing. Nitazoxanide has shown efficacy in healthy hosts but has not been shown to be superior to placebo in the severely immunocompromised [93-95]. If used, nitazoxanide is given at a dose of 500 mg bd for 3 days, but may be required for up to 12 weeks. Paromomycin has shown little effect on symptoms and oocyst shedding in two randomised placebo-controlled trials [96,97]. A study combining paromomycin with azithromycin demonstrated substantial reduction in stool frequency and volume [98]. Additional supportive measures such as rehydration, electrolyte replacement, nutritional support and anti-motility agents may be required.

Impact of cART
The use of optimised cART should be continued to prevent relapse.

Prevention

Initiation of cART prior to advanced immunosuppression should prevent the development of cryptosporidiosis. Patients with CD4 counts <200 cells/mm^3 should avoid drinking untreated water and ensure careful hand hygiene. Standard drinking water chlorination techniques are not sufficient to eradicate the parasite. Specific filtration employing an 'absolute' 1-μm filter is required [99]. Bottled water is not necessarily a safer option and boiling of water should be advocated.

4.4.4.3. *Microsporidia* spp.

Background and epidemiology
The microsporidia are a group of over 1200 small, spore-forming parasitic fungi. They infect a wide range of vertebrate and invertebrate hosts with at least 14 microsporidia species recognised as human pathogens [100]. Clinical microsporidiosis is most frequently seen in the severely immunosuppressed, particularly in PLWH with a CD4 count <100 cells/mm^3 [101,102]. Cases have also been reported in transplant recipients, those undergoing chemotherapy, diabetics, children, the elderly, travellers and wearers of contact lenses [100]. GI infection occurs following ingestion of microsporidial spores in contaminated water or via contact with infected faeces or urine.

The microsporidia most commonly linked to GI illness are *Enterocytozoon bieneusi* and *Encephalitozoon* (formerly *Septata*) *intestinalis.* These microsporidia both infect villus epithelial cells of the small intestine but *E. intestinalis* has a propensity to disseminate elsewhere in the body, particularly the kidneys, skin, nasal mucosa, eyes and gallbladder [103].

Presentation
Watery, non-bloody diarrhoea, with associated malabsorption, is the most common presentation of GI infection with microsporidia. Sclerosing cholangitis may occur. Dissemination can lead to encephalitis, sinusitis, myositis and renal and ocular infection.

Diagnosis

- *In the diagnosis of microsporidial infection, three stool samples should be examined with chromotrope and chemofluorescent stains (**Grade** 1C).*
- *Where available PCR should be used to aid diagnosis (**Grade** 1B).*
- *A small bowel biopsy may be considered if stool samples are consistently negative (**Grade** 2C).*

Examination of three stool samples with chromotope and chemoflurescent stains for microsporidial spores is often sufficient for diagnosis. Stool microscopy does not allow for speciation and electron microscopy remains the gold standard for confirmation and speciation. Where available PCR is a highly sensitive and specific tool for diagnosis and speciation [104]. If stool samples are consistently negative a small bowel biopsy may be considered [105].

Treatment

- *Effective cART is the first-line treatment for microsporidiosis (**Grade 1C**).*
- *Albendazole can be used in addition to cART in* E. intestinalis *(**Grade 2C**).*

Early initiation of cART is the mainstay of treatment for microsporidiosis and is associated with complete resolution of GI symptoms following restoration of immune function [92,106].

There is no specific therapeutic agent for the treatment of *E. bieneusi.* There may be a response to oral fumagillin (20 mg tds for 14 days) but with significant haematological toxicity [107,108]. *Encephalitozoon* spp. including *E. intestinalis* are susceptible to albendazole (400 mg bd for 21 days) and this drug is recommended for initial therapy in addition to cART. Longer therapy may be required in sites outside the GI tract or in severe disease until immune reconstitution occurs. Nitazoxanide and itraconazole have also been used with variable effectiveness. Thalidomide may be effective for symptom control in some patients [109]. Additional supportive measures such as rehydration, electrolyte replacement, nutritional support and anti-motility agents may be required.

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

Prevention
Initiation of cART prior to advanced immunosuppression should prevent the development of microsporidiosis. Patients with CD4 counts <200 cells/mm^3 should avoid drinking untreated water and ensure careful hand hygiene.

4.4.4.4 Other parasites and helminths that cause diarrhoea

A number of parasites and helminths are found more frequently in PLWH due to overlapping global distribution and the possibility of sexual transmission in MSM.

Giardiasis
Giardiasis is caused by the flagellate parasite *Giardia lamblia.* Infection can be asymptomatic or present with chronic diarrhoea and constitutional symptoms. GI symptoms include nausea, bloating, cramp-like abdominal pain, indigestion and belching. Prolonged diarrhoea may result in a malabsorptive state. Giardiasis is treated with metronidazole (400 mg tds po for 7 days or 1 g od for 3 days) or tinidazole (500 mg bd po for 7 days or 2 g od). Some studies in countries where *G. lamblia* is endemic have shown a decline in incidence of giardiasis with the use of cART [110].

Amoebiasis
Entamoeba histolytica is a protozoan parasite that causes infection following ingestion of cysts in contaminated human faeces. Sexual transmission also occurs and among PLWH; entamoeba infection is most commonly seen in MSM [111]. Following ingestion, *E. histolytica* trophozoites adhere to colonic epithelial cells. Invasion through the mucosa and into the submucosal tissue results in amoebic colitis. Occasionally haematogenous spread

occurs once the trophozoites have breached the colonic mucosa resulting in extra-intestinal disease, most commonly amoebic liver abscess.

E. histolytica infection can be asymptomatic and resolve without intervention, although up to 10% of those with asymptomatic infection will develop disease within a year [112]. Fever, abdominal pain and either watery or bloody diarrhoea are the most common symptoms of amoebic colitis. It occurs in PLWH with a range of CD4 counts and is not limited to those with advanced immunosuppression. Liver abscess can present with fever, right upper quadrant pain and tenderness, usually over a number of days although a chronic presentation with fever and anorexia may also be seen [113].

At least three stool samples should be examined for cysts and trophozoites. However the cysts of *E. histolytica* cannot be differentiated from non-pathogenic *Entamoeba dispar* by microscopy and diagnosis is difficult unless erythrophagocytosis (ingestion of red blood cells) by motile trophozoites is seen. Antigen-based enzyme-linked immunosorbent assays (ELISAs) may also be used but PCR is the method of choice in the UK for the diagnosis of both symptomatic and asymptomatic infection [114]. Serology remains positive for years after exposure but can be valuable in the diagnosis of extra-intestinal lesions when combined with imaging.

Metronidazole 800 mg tds po for 5–10 days is the regimen of choice for treating amoebic colitis and amoebic liver abscess. Tinidazole 2 g od po for 3 days is an alternative treatment option. Metronidazole and tinidazole are relatively ineffective against *E. histolytic* cysts within the gut, therefore patients should receive diloxanide furoate 500 mg tds po for 10 days following treatment with metronidazole to eliminate luminal infection.

Cyclosporiasis
Cyclospora cayetanensis is an intestinal coccidian protozoal parasite of the small bowel. It is a cause of watery diarrhoea throughout the tropics and sub-tropics and in returning travellers. In PLWH, diarrhoea may be prolonged and biliary involvement has also been reported [115,116].

Diagnosis is made by the microscopic detection of oocystes in stool specimens. A wet preparation and concentration technique should be used followed by examination under ultraviolet light for parasite autoflurescence or confirmed using modified Ziehl-Neelsen staining and accurate measurement. PCR can aid in diagnosis and specimens should be referred to the Public Health England National Reference Laboratory, Hospital for Tropical Diseases, for confirmation and typing [117]. The clinical and parasitological response to co-trimoxazole 960 mg bd is rapid and 7 days of treatment is usually sufficient [118]. Relapse is common and secondary prophylaxis with co-trimoxazole 960 mg three times a week may be needed while cART is commenced.

Cystoisosporiasis (isosporiasis)
Isospora belli has no known animal host but is widespread geographically and causes self-limiting diarrhoea in HIV-seronegative individuals. In PLWH it can cause chronic diarrhoea and is an occasional cause of biliary disease. It is diagnosed by identification of oocysts in stool specimens using microscopy with modified Ziehl-Neelsen staining [119]. The

traditional treatment has been co-trimoxazole 960 mg four times daily po for 10 days although 960 mg bd appears also to be effective [118]. Secondary prophylaxis with co-trimoxazole 960 mg three times a week is essential as relapse is common. Ciprofloxacin is a less effective alternative for both treatment and prophylaxis [120].

Strongyloidiasis

Strongyloides stercoralis is a gut nematode that causes chronic GI and skin disorders due to its autoinfective lifecycle and can disseminate to cause life-threatening hyperinfection syndromes in immunosuppressed individuals [121-124]. Despite anecdotal reports, there is no conclusive evidence that infection or hyperinfection is more common in PLWH, although it may be implicated in immune reconstitution syndrome [125]. Corticosteroid use appears to be a causative factor in case reports of hyperinfection syndrome in PLWH [126]. Eosinophilia is common and is diagnosed by identification of larvae in stool specimens following culture. Serology may also be useful. First-line treatment of choice is ivermectin 200 μg/kg od po for 1 or 2 days, which is more effective than the alternative treatment of albendazole 400 mg bd po for 3 days. Examination of stool samples should be repeated at 2–4 weeks to confirm clearance of infection with a further course of ivermectin if there is any concern of residual infection. Hyperinfection requires the course of ivermectin to be continued for at least 14 days, with the Centres for Disease Control and Prevention recommending continuation for 2 weeks after stool and/or sputum examination are negative [127]. Serology and stool examination should be repeated at intervals of 6–12 months over the first 2 years after treatment, as autoinfective migrating larvae may not be eradicated by initial treatment.

Schistosomiasis

Schistosomiasis is a chronic inflammatory disease caused by a parasitic blood fluke. There are three main species that cause human disease: *Schistosoma haematobium*, found throughout Africa, parts of the Middle East and Mauritius, *S. mansoni*, found in Africa, parts of South America and the Caribbean, and *S. japonicum*, found in China and parts of South East Asia. Infection occurs following contact with contaminated freshwater bodies. Some people experience a short, self-limiting febrile illness following initial infection; many with chronic schistosomiasis are asymptomatic. Those with heavy or repeated infection can experience disease as a consequence of inflammation triggered by eggs produced by the adult worms. *S. mansoni* and *S. japonicum* occupy the lower mesenteric veins resulting in urogenital disease whereas *S. haematobium* inhabit the venus plexus resulting in hepatic and GI disease.

Infection with schistosomiasis is not believed to occur more frequently in PLWH although urogenital schistosomiasis is thought to increase HIV acquisition in women. Accelerated progression of HIV has also been observed in those co-infected with schistosomiasis [128,129]. Examination of the faeces and urine for eggs is the primary method for diagnosis. Serology can be useful in those with potential exposure who have not previously been treated. However, serology cannot distinguish between past or current infection and has a window period of 8–12 weeks following exposure before a test may be positive. Schistosomiasis can be effectively treated with praziquantel, with dosing determined by species.

4.4.5 Fungal infections

Candidiasis, histoplasmosis, cryptococcosis, aspergillosis, paracoccidiodomycosis, pneumocystis and talaromycosis (formerly penicilliosis) have been reported as rare causes of lower GI tract infection in PLWH. These mycoses have usually been described in PLWH with low CD4 counts and as disseminated infections. Diagnosis may be established using specific tests such as blood culture or antigen tests, however colonoscopic biopsy may be necessary to establish the diagnosis. Treatment for these mycoses is described in other chapters.

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Appendix 1. Literature searching and PICO questions

Literature searching

The PubMed database was searched using the following terms:

(HIV OR AIDS) AND: CMV colitis OR (CMV AND gastrointestinal disease) OR (CMV AND diarrhoea) OR (CMV AND loose stools)

(HIV OR AIDS) AND: campylobacter OR clostridium difficile OR E coli OR salmonella OR shigella OR mycobacterium tuberculosis OR mycobacterium avium-intracellulare complex OR mycobacterium kansaii OR chlamydia trachomatis OR lymphogranuloma venereum

(HIV OR AIDS) AND: diarrh* OR gastroenteritis OR bacterial diarrh* OR viral diarrh*

PICO questions

The literature searches were based on the following PICO questions:

What is the best method for diagnosing oropharyngeal candidiasis?
When should endoscopy be considered in PLWH with oesophageal disease?
What are the best diagnostic tests for CMV and HSV in PLWH?
Which is the best treatment for CMV oesophagitis or colitis in PLWH?
What is the best treatment for oropharyngeal or oesophageal HSV infection?
What are the clinical presentations of CMV infection in PLWH?
Which virological method is used to diagnose GI infection secondary to CMV infection in PLWH?
Is CMV prophylaxis beneficial in PLWH with CD4 counts below 100 cells/mm^3?
What is the best treatment for CMV colitis in PLWH?
What is the best treatment for ganciclovir-resistant CMV colitis in PLWH?

How does cryptosporidium present in PLWH?
What is the best diagnostic test for cryptosporidium in PLWH?
How should cryptosporidium be treated in PLWH?

How does microsporidia infection present in PLWH?
What is the best diagnostic test for microsporidia infection in PLWH?
How should microsporidia infection be treated in PLWH?

How does giardia infection present in PLWH?
How should giardia infection be treated in PLWH?
Is giardia seen more commonly in PLWH?

How does amoebiasis present in PLWH?
What is the best diagnostic test for amoebiasis in PLWH?
How should amoebiasis be treated in PLWH?

How does isosporiasis present in PLWH?

How should isosporiasis be diagnosed in PLWH?
How should isosporiasis be treated in PLWH?

Is HIV a cause of hyperinfection in strongylodiasis?
What is the best diagnostic test for strongoloidiasis in PLWH?
How should infection with strongyloides be treated in PLWH?

Is infection with schistosomiasis more common in PLWH?
What is the best diagnostic test for schistosomiasis?
How should schistosomiasis be treated?

What causes diarrhoea in PLWH?
Which bacteria cause diarrhoea in PLWH?
Which viruses cause diarrhoea in PLWH?

How does *C. difficile* present in PLWH?
What are the risk factors for C. *difficile* in PLWH?
How is C. *difficile* treated in PLWH?

How does campylobacter present in PLWH?
What are the risk factors for campylobacter in PLWH?
How is campylobacter treated in PLWH?

How does *E. coli* present in PLWH?
What are the risk factors for *E. coli* in PLWH?
How is *E. coli* treated in PLWH?

How does salmonella present in PLWH?
What are the risk factors for salmonella in PLWH?
How is salmonella treated in PLWH?

How does shigella present in PLWH?
What are the risk factors for shigella in PLWH?
How is shigella treated in PLWH?

How does viral gastroenteritis present in PLWH?
What are the risk factors for viral gastroenteritis in PLWH?
How is viral gastroenteritis treated in PLWH?

Appendix 2. Summary of the modified GRADE system

BHIVA revised and updated the Association's guideline development manual in 2011 [1]. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations [2,3].

1A Strong recommendation. High-quality evidence. Benefits clearly outweigh risk and burdens, or vice versa. Consistent evidence from well-performed, randomised controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. Strong recommendations, can apply to most individuals in most circumstances without reservation. Clinicians should follow a strong recommendation unless there is a clear rationale for an alternative approach.	**2A** Weak recommendation. High-quality evidence. Benefits closely balanced with risks and burdens. Consistent evidence from well-performed randomised controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. Weak recommendation, best action may differ depending on circumstances or individuals or societal values.
1B Strong recommendation. Moderate-quality evidence. Benefits clearly outweigh risk and burdens, or vice versa. Evidence from randomised controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise), or very strong evidence of some other research design. Further research may impact on our confidence in the estimate of benefit and risk. Strong recommendation and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.	**2B** Weak recommendation. Moderate-quality evidence. Benefits closely balanced with risks and burdens, some uncertainly in the estimates of benefits, risks and burdens. Evidence from randomised controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise). Further research may change the estimate of benefit and risk. Weak recommendation, alternative approaches likely to be better for some individuals under some circumstances.
1C Strong recommendation. Low-quality evidence. Benefits appear to outweigh risk and burdens, or vice versa. Evidence from observational studies, unsystematic clinical experience or from randomised controlled trials with serious flaws. Any estimate of effect is uncertain. Strong recommendation, and applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.	**2C** Weak recommendation. Low-quality evidence. Uncertainty in the estimates of benefits, risks and burdens; benefits may be closely balanced with risks and burdens. Evidence from observational studies, unsystematic clinical experience or from randomised controlled trials with serious flaws. Any estimate of effect is uncertain. Weak recommendation; other alternatives may be reasonable.
1D Strong recommendation. Very low-quality evidence. Benefits appear to outweigh risk and burdens, or vice versa. Evidence limited to case studies. Strong recommendation based only on case studies and expert judgement.	**2D** Weak recommendation. Very low-quality evidence. Uncertainty in the estimates of benefits, risks and burdens; benefits may be closely balanced with risks and burdens. Evidence limited to case studies and expert judgement. Very weak recommendation; other alternatives may be equally reasonable.

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