

British HIV Association guidelines on the management of opportunistic infection in people living with HIV: The clinical management of gastrointestinal opportunistic infections 2020 (2022 interim update)

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Keywords: *colitis, diarrhoea, gastrointestinal opportunistic infection, oesophagitis*

1 Methods

The scope, purpose and guideline topics were agreed by the writing group. The search (population, intervention, comparator and outcome [PICO]) questions were set and an independent systematic literature review carried out. The PubMed, Medline, Embase and Cochrane Library databases were searched and the literature reviewed to address each question. The PICO questions and search strategies are outlined in Appendix 1.

Further details of the methodology can be found on the British HIV Association (BHIVA) website (<https://www.bhiva.org/file/5d514ec9b503d/OI-guidelines-methods-general.pdf>), including the use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess and grade the evidence.

2 General overview

Gastrointestinal (GI) symptoms occur frequently in people living with HIV. Dysphagia and diarrhoea (Table 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 people living with HIV take combination antiretroviral therapy (cART), however there remain some differences in type of pathology seen compared to non-HIV-positive populations, and opportunistic infections may still occur in those with higher CD4 counts [1]. If a cause of persisting GI symptoms is not apparent, consultation with a gastroenterologist is indicated because people living with HIV 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].

Guidance on supporting patients living with HIV with opportunistic infections, including GI infections, can be found on the BHIVA website (<https://www.bhiva.org/file/6225e44b53c49/OI-guidelines-supporting-patients.pdf>).

3 Summary of recommendations

5 Oropharyngeal and oesophageal infections

5.3 Diagnosis

- **Oral and oesophageal candidiasis are clinical diagnoses (Grade 1B, moderate quality of 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 of 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 of evidence).**

5.4 Treatment

- **Fluconazole remains the preferred treatment option for oropharyngeal (100–200 mg/day for 7–14 days) or oesophageal (200–400 mg once daily [od] for 14–21 days) candidiasis on the basis of an updated Cochrane database systematic review [7] (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 1B, moderate quality of evidence) [8,9]; 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 1C, low quality of evidence).**
- **Ongoing maintenance therapy for CMV oesophagitis is not routinely indicated, unless there is concomitant ophthalmological disease (Grade 1C, low quality of evidence).**
- **HSV oesophagitis should be treated with aciclovir 5–10 mg/kg three times daily (tds) 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, moderate quality of evidence).**

5.5 Prevention and impact of cART

- **cART is the mainstay of prevention of upper GI tract infections with Candida or herpes viruses (Grade 1B, moderate quality of evidence).**

6 Diarrhoea

6.2 Bacterial gastroenteritis

6.2.3 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 of evidence).**
- **C. difficile toxin assessment and/or culture should be carried out in all PLWH presenting with acute diarrhoea (Grade 1D, very low quality of evidence).**

6.2.4 Treatment

- **Acute bacterial diarrhoea usually does not require treatment in PLWH with CD4 counts ≥ 200 cells/mm³, but should be treated when the CD4 count is < 200 cells/mm³ (Grade 2D, very low quality of evidence).**
- **Acute bacterial diarrhoea should be treated as per sensitivity tests and local guidance (Grade 2D, very low quality of evidence).**
- **C. difficile infection should be treated as per national guidelines (Grade 1A, high quality of evidence).**

6.2.5 Prevention and impact of cART

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

6.3 CMV and viral gastroenteritis

6.3.2 Diagnosis

- **CMV colitis should be diagnosed by biopsy with characteristic features seen on histopathology (Grade 1C, low quality of evidence).**

6.3.3 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, moderate quality of evidence).**

6.3.4 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, moderate quality of evidence).**
- **Valganciclovir (900 mg bd po) may be used for non-severe CMV colitis or when the patient is able to tolerate and absorb oral medication (Grade 1C, low quality of evidence).**
- **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, moderate quality of evidence).**

6.3.5 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 [68] (Grade 2B, moderate quality of evidence).**

- **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 >100 cells/mm³ for more than 6 months (Grade 1C, low quality of evidence).**

6.3.6 Treatment failure

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

6.4 Parasitic and helminth infections

6.4.2 *Cryptosporidium* spp.

Diagnosis

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

Treatment

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

6.4.3. *Microsporidium* spp.

Diagnosis

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

Treatment

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

4 Auditable outcomes

- **Percentage of patients with chronic diarrhoea for whom samples are sent for examination of parasites, ova and cysts, and if a pathogen is isolated, percentage treated with anti-infective agent.**

- Percentage of patients with acute diarrhoea for whom a stool sample is sent for examination, and percentage for whom a pathogen is isolated.
- Percentage of patients with oesophageal symptoms and no oropharyngeal candidiasis who have an upper GI endoscopy.
- Percentage of patients with suspected cytomegalovirus (CMV) colitis who have the diagnosis confirmed by endoscopy and biopsies.

5 Oropharyngeal and oesophageal infections

5.1 Candidiasis

The organisms that most commonly cause oropharyngeal infections and oesophagitis are *Candida* spp. Persistent or recurrent oesophageal candidiasis has decreased in the cART era and most often indicates poor HIV viral control [3]. Candidiasis of the upper GI tract is discussed in detail in a separate chapter of the BHIVA guidelines on the management of opportunistic infection in people living with HIV: The clinical management of Candidiasis 2019 [4].

5.2 Other causes of oropharyngeal and oesophageal 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 CMV infections, which cause ulceration and may coexist with candidiasis, especially in people living with HIV with CD4 counts <100 cells/mm³. Tuberculosis is a rare cause of oesophageal or oropharyngeal disease. Idiopathic ulcers are also common. Primary syphilis can present with oral ulcers as well as causing genital and perianal ulceration. Individuals at risk should be screened in line with national guidelines. 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 people living with HIV [5].

5.3 Diagnosis

- **Oral and oesophageal candidiasis are clinical diagnoses (Grade 1B, moderate quality of 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 of 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 of evidence).**

The results of a randomised trial demonstrated that initial empirical therapy for candidiasis is a reasonable first approach in uncomplicated oesophagitis [6]. 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.

5.4 Treatment

- ***Fluconazole remains the preferred treatment option for oropharyngeal (100–200 mg/day for 7–14 days) or oesophageal (200–400 mg once daily [od] for 14–21 days) candidiasis on the basis of an updated Cochrane database systematic review [7] (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 1B, moderate quality of evidence) [8,9]; 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 1C, low quality of evidence).***
- ***Ongoing maintenance therapy for CMV oesophagitis is not routinely indicated, unless there is concomitant ophthalmological disease (Grade 1C, low quality of evidence).***
- ***HSV oesophagitis should be treated with aciclovir 5–10 mg/kg three times daily (tds) 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, moderate quality of evidence).***

Further discussion of the treatment of candidiasis can be found in the candidiasis chapter of the BHIVA guidelines on the management of opportunistic infection in people living with HIV [4]. Foscarnet 90 mg/kg bd iv may be used in cases of ganciclovir-resistant CMV or 40 mg/kg bd or tds for aciclovir-resistant HSV [10]. 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.

5.5 Prevention and impact of cART

- ***cART is the mainstay of prevention of upper GI tract infections with *Candida* or herpes viruses (Grade 1B, moderate quality of evidence).***

6 Diarrhoea

6.1 Epidemiology of acute diarrhoea

Diarrhoea is common among people living with HIV, even in the era of cART. A meta-analysis of post-2008 clinical trials demonstrated that the prevalence of diarrhoea was 18% among people living with HIV on treatment [11]. 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 likely to be associated with opportunistic infections in people living with HIV than in the general population, particularly those with lower CD4 counts.

Table 1 Major causes of HIV-related diarrhoea

| Bacteria | Parasites and fungi | Viruses | Non-infectious causes |
|---|----------------------------------|-------------|-----------------------------------|
| <i>Campylobacter</i> spp. | <i>Cryptosporidium</i> spp. | CMV | cART |
| <i>Clostridioides difficile</i> | <i>Cyclospora cayetanensis</i> | HSV | Kaposi's sarcoma |
| <i>Escherichia coli</i> (pathotypes) | <i>Giardia lamblia</i> | Rotavirus | Lymphoma |
| <i>Salmonella</i> spp. | <i>Entamoeba histolytica</i> | Norovirus | Pancreatic exocrine insufficiency |
| <i>Shigella</i> spp. | <i>Cystoisospora belli</i> | Adenovirus | |
| <i>Mycobacterium tuberculosis</i> | <i>Microsporidia</i> | Astrovirus | |
| <i>Mycobacterium avium-intracellulare</i> complex | <i>Strongyloides stercoralis</i> | Coronavirus | |
| <i>Mycobacterium kansasii</i> | | | |
| <i>Chlamydia trachomatis</i> / <i>Lymphogranuloma venereum</i> | | | |

6.2 Bacterial gastroenteritis

6.2.1 Aetiology

A range of bacteria commonly cause gastroenteritis in people living with HIV (Table 2). *Clostridioides difficile* was the most common cause of diarrhoea among people living with HIV in a US cohort study [12]. However, this has not been replicated in other studies in high-income countries. *C. difficile* is prevalent in high-income and low-/middle-income countries (LMICs) [13-15] and spans the pre- and post-cART eras [16]. Invasive non-typhoidal salmonellosis (iNTS) was recognised early in the HIV epidemic to be strongly associated with immunosuppression in both high-income countries [17-19] and LMICs [20-22]. As in HIV-negative individuals, other bacterial pathogens causing diarrhoea include *Escherichia coli*, *Campylobacter* spp. and *Shigella* spp. [23-25].

The prevalence of *Shigella* spp. was higher among HIV-positive men who have sex with men (MSM) compared to HIV-negative MSM in the UK [26] and other pathogens such as *Campylobacter* spp. are increasingly identified among HIV-positive MSM [27]. Lymphogranuloma venereum (LGV), caused by *Chlamydia trachomatis*, can be associated with diarrhoea as part of proctocolitis or enteritis syndromes and is increasingly common among MSM in Europe [28,29].

6.2.2 Risk factors

Older age and lower CD4 count increase the likelihood of diarrhoea in people living with HIV [30]. Residence in 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 people living with HIV [13,16].

6.2.3 Presentation and diagnosis

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

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 people living with HIV, but remains uncommon overall [31,32]. In people living with HIV, iNTS infections present with febrile illness or sepsis syndromes, and diarrhoea may be absent or a less prominent feature [22]. Presenting symptoms of *C. difficile* infection in people living with HIV are similar to those in HIV-negative individuals [33,34]. Data from case series suggest that *C. difficile* infection is no more severe in people living with HIV [35,36]. 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 [26].

Table 2 Diagnosis and treatment of selected bacterial infections

| Bacteria | Association with HIV | Diagnosis | Treatment | Impact of cART |
|-----------------------------------|----------------------------|---|---|---|
| <i>Campylobacter</i> spp. | Indeterminate/yes with MSM | Stool culture (preferred) or molecular test | If CD4 \geq 200 cells/mm ³ , usually no treatment required; if CD4 <200 cells/mm ³ , treat with azithromycin as per local guidelines | May reduce likelihood of future infection |
| <i>Clostridioides difficile</i> | Yes/intermediate | Molecular test, EIA-GDH, EIA for toxins A + B, toxigenic culture (as per local guidelines), colonoscopy + biopsy, CT scan | As per national guidelines [37] | Reduces likelihood of future infection |
| <i>Escherichia coli</i> | Indeterminate/yes | Stool culture (preferred) EIA for Shiga toxin or molecular test | 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 |
| <i>Salmonella</i> spp. | Indeterminate/yes | Stool culture (preferred) or molecular test | If CD4 \geq 200 cells/mm ³ , usually no treatment required; if CD4 <200 cells/mm ³ , treat with ciprofloxacin or ceftriaxone as per local guidelines | May reduce likelihood of future infection |
| <i>Shigella</i> spp. | Indeterminate/yes with MSM | Stool culture (preferred) or molecular test | If CD4 \geq 200 cells/mm ³ , usually no treatment required; if CD4 <200 cells/mm ³ , treat with ciprofloxacin or azithromycin as per local guidelines | May reduce likelihood of future infection |
| <i>Mycobacterium tuberculosis</i> | Indeterminate | Colonoscopy + biopsy for histology (AFB smear) + mycobacterium culture (preferred to molecular test for intestinal | See BHIVA guidelines on management of tuberculosis in adults living with HIV 2018 [38] | May reduce likelihood of future infection |

| | | | | |
|------------------------------------|---------------|--|---|--|
| | | tuberculosis); intestinal tissue molecular test, CT preferred mode of imaging | | |
| <i>Mycobacterium avium</i> complex | Yes | Definitive diagnosis requires culture in blood or from bone marrow aspirate or fluid from a normally sterile site or biopsy specimen | See separate chapter on the treatment of <i>Mycobacterium avium</i> complex in the BHIVA/British Infection Association (BIA) guidelines for the treatment of opportunistic infection in HIV [39]* | May reduce likelihood of future infection |
| <i>Mycobacterium kansasii</i> | Indeterminate | Colonoscopy + biopsy for histology (AFB smear) + mycobacterium culture (preferred to molecular test for intestinal tuberculosis); intestinal tissue molecular test, CT preferred mode of imaging | See separate chapter on the treatment of <i>Mycobacterium kansasii</i> in the BHIVA/BIA guidelines for the treatment of opportunistic infection in HIV [39]* | May reduce likelihood of future infection |
| <i>Chlamydia trachomatis</i> /LGV | Yes with MSM | Rectal swab molecular test, if <i>C. trachomatis</i> positive then test DNA for LGV-specific serovars | As per national guidelines [40]: 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. Molecular tests include PCR, reverse transcription (RT)-PCR and quantitative RT-PCR.

*The *Mycobacterium avium* complex/*Mycobacterium kansasii* chapter of the BHIVA/BIA guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011 is currently being revised.

6.2.4 Treatment

- **Acute bacterial diarrhoea usually does not require treatment in people living with HIV with CD4 counts ≥ 200 cells/mm³, but should be treated when the CD4 count is < 200 cells/mm³ (Grade 2D, very low quality of evidence).**
- **Acute bacterial diarrhoea should be treated as per sensitivity tests and local guidance (Grade 2D, very low quality of evidence).**
- ***C. difficile* infection should be treated as per national guidelines (Grade 1A, high quality of evidence).**

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. [41-43] 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 [37]: for non-severe *C. difficile* infection metronidazole is currently indicated, and severe infection should be treated with vancomycin or fidaxomicin considered in those who are at high risk of recurrence [37,44]. There is no evidence for the use of probiotics for *C. difficile* treatment [45]. The treatment response for people living with HIV and HIV-negative people appears similar and complications do not appear to be more or less common in people living with HIV. For recurrent *C. difficile* infection, treat with fidaxomicin or vancomycin; a tapering therapy may be considered [37]. Faecal transplant may be considered and can be effective in the general population [46-48]. Based on data from case reports and case series, donor stool transplant appears to be safe and effective in people living with HIV, including those with a low CD4 count [47].

A Cochrane review of 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 [44]. 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.

6.2.5 Prevention and impact of cART

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

Trimethoprim-sulphamethoxazole (co-trimoxazole) reduced the incidence of infectious diarrhoea in the pre-cART era [49]. The introduction of cART has been more effective than antimicrobial prophylaxis in preventing recurrence of non-typhoidal salmonella [50,51]. If given, the duration of antimicrobial prophylaxis, with agents such as fluoroquinolones, need not exceed 30 days in patients established on cART [52].

The incidence of bacterial diarrhoea has declined steadily since the introduction of cART, therefore cART is the mainstay of preventing bacterial diarrhoea [53,54]. Co-trimoxazole is no longer recommended for prevention of bacterial diarrhoea.

6.3 CMV and viral gastroenteritis

6.3.1 Background

A variety of viruses can cause gastroenteritis in people living with HIV (Table 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 people living with HIV, especially among MSM. CMV is still the most common opportunistic pathogen causing viral enteritis in people living

with HIV although the incidence has decreased substantially in the cART era [55]. Most cases of CMV disease occur in people with prior CMV infection and a CD4 cell count <50 cells/mm³ [56].

People living with HIV often present with non-specific GI symptoms. Although it can affect the entire GI tract, CMV infection frequently involves the oesophagus or the colon [57,58]. 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 cytopenias. 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 the presence of retinitis. If present, CMV treatment should be initiated and cART initiation delayed – typically by 2 weeks – to reduce the risk of immune reconstitution inflammatory syndrome [59,60]. If initial examination is negative, direct fundoscopy and ophthalmology review should be repeated if any visual symptoms occur. 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.

6.3.2 Diagnosis

- ***CMV colitis should be diagnosed by biopsy with characteristic features seen on histopathology (Grade 1C, low quality of evidence).***

The diagnosis of CMV-associated GI 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 [61-63].

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

Table 3 Diagnosis and treatment of selected viral infections

| Virus | Association with HIV | Diagnosis | Treatment | Impact of cART |
|-------|----------------------|--|--|--|
| CMV | Yes | Biopsies + histology (if GI symptoms) from upper or lower GI endoscopy; CMV molecular test | Ganciclovir (5 mg/kg bd iv) 2–4 weeks/until symptom resolution. For non-severe infection, oral valganciclovir (900 mg bd) may be used. Second line: foscarnet (90 mg/kg bd iv) for 2 weeks | Reduces likelihood of future infection |

| | | | | |
|-------------|------------------|--|---|---|
| HSV | Indeterminate | Rectal swab molecular test for HSV | As per national guidelines [64]: aciclovir 400 mg tds or valaciclovir 500 mg bd | May reduce likelihood of recurrence |
| Rotavirus | No/indeterminate | ELISA, latex agglutination or molecular test (preferred method) | Supportive measures | May reduce likelihood of future infection |
| Norovirus | No | Molecular test (preferred method), ELISA | Supportive measures | Nil |
| Adenovirus | Indeterminate | Molecular test, EIA, histology (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 | Molecular test, EIA | Supportive measures | May reduce likelihood of future infection |
| Coronavirus | No/indeterminate | Molecular test (preferred), EIA | Supportive measures | May reduce likelihood of future infection |

ELISA, enzyme-linked immunosorbent assay. Molecular tests include PCR, RT-PCR and quantitative RT-PCR.

6.3.3 Primary prophylaxis

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

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

6.3.4 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, moderate quality of evidence).***
- ***Valganciclovir (900 mg bd po) may be used for non-severe CMV colitis or when the patient is able to tolerate and absorb oral medication (Grade 1C, low quality of evidence).***
- ***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, moderate quality of evidence).***

Ganciclovir is the preferred treatment for induction therapy for CMV colitis [65]. Foscarnet is also effective but ganciclovir is the preferred agent because of fewer side effects [66]. 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 [67].

6.3.5 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 [68] (Grade 2B, moderate quality of evidence).**
- **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 >100 cells/mm³ for more than 6 months (Grade 1C, low quality of evidence).**

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

6.3.6 Treatment failure

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

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. An 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 (>10⁶ IU/mL) are risk factors for resistance.

In cases of relapsed CMV retinitis, treatment options include ganciclovir plus foscarnet [69] 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 [70]. 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) [71-73]. 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 [74]. Novel anti-CMV therapies are becoming available including marabavir, which has a potential role in refractory or resistant CMV infection in haematopoietic cell or solid organ transplant recipients [75], and letermovir, which has a role in CMV prophylaxis after transplantation in CMV-seropositive recipients [76]. These agents could be acquired on a named patient basis, but currently there is a lack of evidence for clinical use in people living with HIV.

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 include advanced age, certain comorbidities and concomitant nephrotoxic medications [77]. Reports of renal toxicity associated with concurrent use of ganciclovir/valganclovir and tenofovir have been published [78].

6.3.7 Other viral infections

HSV, adenovirus, norovirus, astrovirus and rotavirus have also been implicated in the causation of viral enteritis in people living with HIV and there is some suggestion of increased severity in this population [79-81]. Only HSV, which more commonly affects the oesophagus, has established treatment options (see treatment of HSV oesophagitis above). Cidofovir shows activity against adenovirus although cases of clinically significant colitis caused by this virus are rarely reported [82]. There have been reports implicating coronavirus, which may coexist with bacterial pathogens [83] in acute diarrhoea, and adenovirus, which may coexist with CMV in patients with chronic diarrhoea [84]. 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 people living with HIV. MSM and others who have anal sex are at risk of sexually acquired diarrhoeal disease [26].

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 of the BHIVA opportunistic infection guidelines.

The incidence of viral opportunistic infections has declined following the introduction of cART [54], and cART is the mainstay of preventing viral diarrhoea.

6.4 Parasitic and helminth infections

6.4.1 Background

A number of parasites and helminths can cause GI pathology in people living with HIV (Table 4), and their diagnosis and treatment are summarised below.

Table 4 Diagnosis and treatment of selected parasitic infections

| Parasite | Association with HIV | Diagnosis | Treatment | Impact of cART |
|-----------------------------|----------------------|---|---|---|
| <i>Cryptosporidium</i> spp. | Yes | Faecal microscopy or molecular test. 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 |
| <i>Microsporidium</i> spp. | Yes | Faecal microscopy with chromotrope and | Effective cART. Albendazole 400 mg bd for 14 days can be | Effective cART essential for treatment and to |

| | | | | |
|----------------------------------|-------------------|--|---|--|
| | | chemofluorescent stains. PCR where available. Small bowel biopsy can be considered | given in addition in <i>Encephalitozoon intestinalis</i> infection | prevent relapse |
| <i>Giardia lamblia</i> | No/indeterminate | Faecal microscopy or molecular test 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 |
| <i>Entamoeba histolytica</i> | No | Faecal microscopy and molecular test. 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 paromomycin 500 mg tds for 10 days or diloxanide furoate 500 mg tds po for 10 days | Nil |
| <i>Cyclospora cayetanensis</i> | 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 |
| <i>Cystoisospora belli</i> | Yes | Faecal microscopy of iodine-, ZN-, auramine- or safranin-methylene blue-stained smears | Co-trimoxazole 960 mg bd po for 7 days. Alternative: co-trimoxazole 960 mg qds for 10 days or ciprofloxacin 500 mg bd followed by the same antibiotic as prophylaxis | Antibiotic prophylaxis required until effective response to cART |
| <i>Strongyloides stercoralis</i> | No/indeterminate | Stool culture to detect larvae in faeces, at duodenal biopsy or using the string test; serology | Ivermectin 200 µg/kg od po for 1 or 2 days. Alternative: albendazole 400 mg bd po for 3 days | Nil |
| <i>Schistosoma</i> spp. | No/indeterminate | Stool or urine microscopy for ova. Serology in those without history of previous treatment; serology | Praziquantel; dose determined by species | Nil |

qds, four times daily; ZN, Ziehl-Neelsen. Molecular tests include PCR, RT-PCR and quantitative RT-PCR.

6.4.2 *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 [85]. Sexual transmission can also occur, particularly via the faecal–oral route [86].

Cryptosporidium is a significant cause of chronic diarrhoea in patients with advanced HIV, of diarrhoea in children and of zoonotic and waterborne outbreaks [87]. People living with HIV are at greatest risk when their CD4 count is <100 cells/mm³ [88]. *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% and the remainder either non-typable or other species [89].

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 people living with HIV with a CD4 count <50 cells/mm³, 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 [90].

As the epithelium of both the pancreatic duct and biliary tract can be infected, cholangitis and pancreatitis may occur in individuals with prolonged infection [91]. 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 [92,93] and raise the possibility of respiratory transmission of cryptosporidiosis [94].

Diagnosis

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

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 stain. 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 [93].

Increasingly UK laboratories are using enzyme immunoassays that have a similar sensitivity and specificity to microscopy with auramine phenol [95,96]. PCR can also be used for the detection and speciation of *Cryptosporidium* with excellent sensitivity and specificity [97].

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 gallbladder wall.

Treatment

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

In advanced HIV, restoration of the immune system with effective cART is associated with full resolution of *Cryptosporidium* infection [98,99]. Although a number of drugs have shown activity *in vitro*, in animal models and in immunocompetent patients, their use in people living with HIV has been disappointing. Nitazoxanide has shown efficacy in healthy hosts but has not been shown to be superior to placebo in those who are severely immunocompromised [100-102]. 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 [103,104]. The results of a study combining paromomycin with azithromycin demonstrated substantial reduction in stool frequency and volume [105]. Additional supportive measures such as rehydration, electrolyte replacement, anti-motility agents and referral to a dietician for nutritional support 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/mm³ should avoid drinking unfiltered 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 [106]. Bottled water is not necessarily a safer option and boiling of water should be advocated.

6.4.3. *Microsporidium* 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 species recognised as human pathogens [107]. Clinical microsporidiosis is most frequently seen in individuals who are severely immunosuppressed, particularly in people living with HIV with a CD4 count <100 cells/mm³ [108,109]. Cases have also been reported in transplant recipients, those undergoing chemotherapy, diabetics, children, the elderly, travellers and wearers of contact lenses [107]. 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 species 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 [110].

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, low quality of evidence).*
- *Where available PCR should be used to aid diagnosis (Grade 1B, moderate quality of evidence).*
- *A small bowel biopsy may be considered if stool samples are consistently negative (Grade 2C, low quality of evidence).*

Standard stool microscopy will often not detect *Microsporidia*. Examination of three stool samples with chromotrope and chemofluorescent 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 [111]. If stool samples are consistently negative a small bowel biopsy may be considered [112].

Treatment

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

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 [97,113].

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 [114,115]. *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 for involvement of 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 [116]. 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 microsporidiosis. Patients with CD4 counts <200 cells/mm³ should avoid drinking untreated water and ensure careful hand hygiene.

6.4.4 Other parasites and helminths that cause diarrhoea

A number of parasites and helminths are found more frequently in people living with HIV 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 a single dose of 2 g). The patient should be given advice regarding the need for stringent personal hygiene to prevent person-to-person spread. If symptoms persist after initial treatment a repeated course of first-line therapy is recommended. Household and sexual contacts should be investigated as a possible source of reinfection and treated if appropriate. Secondary lactose intolerance should also be considered. If symptoms persist in travellers to Asia, specialist advice should be sought, given that there is an increasing incidence of treatment failure in this population [117]. Some studies in countries where *G. lamblia* is endemic have shown a decline in incidence of giardiasis with the use of cART [118].

Amoebiasis

Entamoeba histolytica is a protozoan parasite that causes infection following ingestion of cysts in contaminated human faeces. Sexual transmission also occurs, including in people living with HIV; among the latter, entamoeba infection is most commonly seen in MSM [119]. 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 [120]. Fever, abdominal pain and either watery or bloody diarrhoea are the most common symptoms of amoebic colitis. It occurs in people living with HIV 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 [121].

At least three stool samples should be examined for cysts and trophozoites. However the cysts of *E. histolytica* cannot be differentiated from non-pathogenic *E. 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 may also be used

but PCR is the method of choice in the UK for the diagnosis of both symptomatic and asymptomatic infection [122]. 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 paromomycin 25–35 mg/kg/day in three divided doses for 5–10 days or diloxanide furoate 500 mg tds po for 10 days following treatment with metronidazole to eliminate luminal infection.

Cyclosporiasis

Cyclospora cayetanensis is an intestinal coccidian protozoan parasite of the small bowel. It is a cause of watery diarrhoea throughout the tropics and sub-tropics and in returning travellers. In people living with HIV, diarrhoea may be prolonged and biliary involvement has also been reported [123,124].

Diagnosis is made by the microscopic detection of oocysts in stool specimens. A wet preparation and concentration technique should be used followed by examination under ultraviolet light for parasite autofluorescence 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 [125]. The clinical and parasitological response to co-trimoxazole 960 mg bd is rapid and 7 days of treatment is usually sufficient [126]. Relapse is common and secondary prophylaxis with co-trimoxazole 960 mg three times a week may be needed while cART is commenced.

Cystoisosporiasis (isosporiasis)

Cystoisospora belli (formerly known as *Isospora belli*) has no known animal host but is widespread geographically and causes self-limiting diarrhoea in HIV-seronegative individuals. In people living with HIV 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 [127]. The traditional treatment has been co-trimoxazole 960 mg four times daily po for 10 days although 960 mg bd also appears to be effective [126]. 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 [128].

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 [129-132]. Despite anecdotal reports, there is no conclusive evidence that infection or hyperinfection is more common in people living with HIV, although it may be implicated in immune reconstitution syndrome [133]. Corticosteroid use appears to be a causative factor in case reports of hyperinfection syndrome in people living with HIV [134]. Eosinophilia is common and infection is diagnosed by identification of larvae in stool specimens following culture. Serology may also be useful

although there may be cross-reaction with other parasitic nematode infections. Discussion with a specialist is recommended prior to treatment of suspected strongyloidiasis due to the potential for complications if alternative nematode infections are present. 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 [135]. Caution should be taken in treating with ivermectin when infection is diagnosed by serology, as cross-reaction with filaria is possible, with the risk of encephalopathy. 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 Centers for Disease Control and Prevention recommending continuation for 2 weeks after negative stool and/or sputum examination results [136]. 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 3–8 weeks 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*, *S. japonicum* and occasionally *S. haematobium* occupy the lower mesenteric veins resulting in intestinal or hepatosplenic disease, whereas *S. haematobium* usually inhabits the venous plexus resulting in urogenital disease.

Infection with schistosomiasis is not believed to occur more frequently in people living with HIV 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 [137,138]. 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.

6.5 Fungal infections

Candidiasis, histoplasmosis, cryptococcosis, aspergillosis, paracoccidioidomycosis, pneumocystis and talaromycosis (formerly penicilliosis) have been reported as rare causes of lower GI tract infection in people living with HIV. These mycoses have usually been described in people living with HIV 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 of the BHIVA opportunistic infection guidelines.

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8 Acknowledgements

The writing group thanks the BHIVA Guidelines Subcommittee for review of the guidelines and helpful comments: N Gupta (Chair), C van Halsema (Vice-chair), A Bailey, T Barber, D Churchill, Y Gilleece, A Grant, S Khoo, A Maxwell, S Parry, A Pozniak, M Rattue (UK Community Advisory Board), I Reeves, H Taha, J Thornhill, L Waters, A Winston.

Appendix 1. Literature searching and PICO questions

Literature searching

The PubMed, Medline, Embase and Cochrane Library databases were searched using the following terms:

(HIV OR AIDS) AND (diarrh* OR gastroenteritis OR gastrointestinal disease OR loose stool* OR oropharyng* OR (o)esophag*)

(HIV OR AIDS) AND (diarrh* OR gastroenteritis OR gastrointestinal disease OR loose stool* OR oropharyng* OR (o)esophag*) AND (CMV OR cytomegalovirus OR CMV colitis OR human herpesvirus 5 or herpes simplex virus)

(HIV OR AIDS) AND (diarrh* OR gastroenteritis OR gastrointestinal disease OR loose stool* OR oropharyng* OR (o)esophag*) AND (campylobacter OR clostridium difficile OR C. difficile OR Escherichia coli OR E coli OR salmonella OR shigella OR candida OR candidiasis OR cryptosporidi* OR microsporidi* OR giardia* OR am(o)ebiasis OR isosporiasis or cystoisospor* or strongyloid* or schistosom* or bilharzia)

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 people living with HIV with oesophageal disease?
- What are the best diagnostic tests for CMV and HSV infection in people living with HIV?
- Which is the best treatment for CMV oesophagitis or colitis in people living with HIV?
- What is the best treatment for oropharyngeal or oesophageal HSV infection?
- What are the clinical presentations of CMV infection in people living with HIV?
- Which virological method is used to diagnose GI infection secondary to CMV infection in people living with HIV?
- Is CMV prophylaxis beneficial in people living with HIV with CD4 counts <100 cells/mm³?
- What is the best treatment for CMV colitis in people living with HIV?
- What is the best treatment for ganciclovir-resistant CMV colitis in people living with HIV?

- How does cryptosporidiosis present in people living with HIV?
- What is the best diagnostic test for cryptosporidiosis in people living with HIV?
- How should cryptosporidiosis be treated in people living with HIV?

- How does microsporidiosis present in people living with HIV?
- What is the best diagnostic test for microsporidiosis in people living with HIV?
- How should microsporidiosis be treated in people living with HIV?

- How does *Giardia* infection present in people living with HIV?
- How should *Giardia* infection be treated in people living with HIV?
- Is *Giardia* infection seen more commonly in people living with HIV?

- How does amoebiasis present in people living with HIV?
- What is the best diagnostic test for amoebiasis in people living with HIV?

How should amoebiasis be treated in people living with HIV?

How does isosporiasis present in people living with HIV?

How should isosporiasis be diagnosed in people living with HIV?

How should isosporiasis be treated in v?

Is HIV a cause of hyperinfection in strongyloidiasis?

What is the best diagnostic test for strongyloidiasis in people living with HIV?

How should strongyloidiasis be treated in people living with HIV?

Is schistosomiasis more common in people living with HIV?

What is the best diagnostic test for schistosomiasis?

How should schistosomiasis be treated?

What causes diarrhoea in people living with HIV?

Which bacteria cause diarrhoea in people living with HIV?

Which viruses cause diarrhoea in people living with HIV?

How does *C. difficile* infection present in people living with HIV?

What are the risk factors for *C. difficile* infection in people living with HIV?

How is *C. difficile* infection treated in people living with HIV?

How does *Campylobacter* infection present in people living with HIV?

What are the risk factors for *Campylobacter* infection in people living with HIV?

How is *Campylobacter* infection treated in people living with HIV?

How does *E. coli* infection present in people living with HIV?

What are the risk factors for *E. coli* infection in people living with HIV?

How is *E. coli* infection treated in people living with HIV?

How does *Salmonella* infection present in people living with HIV?

What are the risk factors for *Salmonella* infection in people living with HIV?

How is *Salmonella* infection treated in people living with HIV?

How does *Shigella* infection present in people living with HIV?

What are the risk factors for *Shigella* infection in people living with HIV?

How is *Shigella* infection treated in people living with HIV?

How does viral gastroenteritis present in people living with HIV?

What are the risk factors for viral gastroenteritis in people living with HIV?

How is viral gastroenteritis treated in people living with HIV?