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British HIV Association and British Infection Association Guidelines for the Treatment of Opportunistic Infection in HIV-seropositive Individuals 2011

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British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011

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1 Introduction

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Keywords: guidelines, opportunistic infections, antiretroviral therapy

Advances in the treatment of HIV infection with antiretroviral therapy have led to dramatic reductions in opportunistic infections and death. However, late presentation of HIV remains a problem and is a significant contributory cause to death in HIV-seropositive persons in the UK [1]. Furthermore, a recent UK Health Protection Agency (HPA) analysis showed that of 46 700 patients with diagnosed HIV, 19% had CD4 counts <200 cells/μL [2] and therefore remain at significant risk of opportunistic infection.

These guidelines have been drawn up to help physicians investigate and manage HIV-seropositive patients suspected of, or having an opportunistic infection (OI). They are primarily intended to guide practice in the UK and related health systems. Although it is hoped they can provide some guidance in developed countries there are some important distinctions in this environment and individual recommendations may not be as applicable in this setting. The early chapters of these guidelines consider the most common presentations of OI disease such as respiratory, gastrointestinal and neurological disease. These chapters are followed by chapters on specific organisms such as *Candida* spp, herpes simplex virus and varicella zoster virus, whilst the final chapters discuss special circumstances such as pregnancy, the use of the intensive care unit, the investigation of unwell patients with fever of undetermined origin and management of imported infections.

Each section contains specific information on the background, epidemiology, presentation, treatment and prophylaxis of OIs.

Since the advent of the era of highly active antiretroviral therapy (HAART) the incidence of 'classic' opportunistic infections such as *Pneumocystis jirovecii* and *Mycobacterium avium* complex has dramatically fallen [3]. The relative contribution of infections that have not formerly been regarded as 'opportunistic' has increased. These include community-acquired pneumonia, *Clostridium difficile* infection and influenza A virus (IAV) infection. The distinction between 'opportunistic' and 'non-opportunistic' infection is becoming blurred. HIV-seropositive individuals are often less immunocompromised than in the era before HAART. Increasingly it is subtle differences in the susceptibility to, or severity of, infections commonly encountered in immunocompetent individuals that are observed in individuals living with HIV. Recent findings suggest that the strains of pneumococci, a pathogen not regarded as 'opportunistic', which are most prevalent in individuals living with HIV behave as 'opportunistic' infections [4]. We accept some infections, such as IAV infection, included in these guidelines are not 'opportunistic', even using this more relaxed view but believe the current concerns relating to IAV infection and evidence that disease may be more severe in some HIV-seropositive individuals [5] justify their inclusion in these guidelines.

Further information on the role of antiretroviral therapy is also discussed (see below). In the appendices there is an A–Z of drugs used in the management of opportunistic infections. This is intended as a guideline but readers are advised to follow the discussion of dosing and the evidence for specific treatments provided in the text. In some cases alternative treatments are provided in the appendix. These are not discussed in the text and these are mainly of historical interest and readers should be aware that these are not, in general, supported by the evidence base for treatments discussed in the text. It should also be noted that as evidence of drug toxicity, interactions, pregnancy risk and cost is rapidly evolving the table should be considered in association with the updated summary of product characteristics (SPC) for the agent and other relevant sources of drug information.

These guidelines have used the British HIV Association (BHIVA) standard grading for levels of evidence (see Table 1.1).

The translation of data into clinical practice is often difficult even with the best possible evidence (i.e. that from two randomized controlled trials) because of trial design,

Table 1.1 Level of evidence

Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well designed quasi-experimental study
III	Evidence obtained from well designed non-experimental descriptive studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

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inclusion criteria and precise endpoints. Furthermore, many opportunistic infection treatment studies were performed prior to the availability of HAART. A number of newer diagnostic tests and imaging modalities may help to expedite OI diagnosis and allow earlier initiation of specific therapy with improved outcomes. Recommendations based upon expert opinion have the least evidence but perhaps provide an important reason for writing the guidelines: to produce a consensual opinion about current practice. It must, however, be appreciated that such opinion is not always correct and alternative practices may be equally valid. The recommendations contained in these guidelines should therefore be viewed as guidelines in the true spirit of the term. They are not designed to be restrictive nor should they challenge research into current practice. Similarly, although the BHIVA Opportunistic Infection Guidelines Group seeks to provide guidelines to optimize treatment, such care needs to be individualized and we have not constructed a document that we would wish to see used as a 'standard' for litigation.

1.1 Antiretroviral therapy

The impact of HAART in preventing opportunistic infection is well established. Whilst HAART is the cornerstone of treatment that leads to resolution or improvement in certain OIs, co-prescription of HAART with specific OI treatment is complicated by overlapping toxicities, drug–drug interactions and occasionally a severe immune reconstitution inflammatory syndrome (IRIS), which may complicate the management of both the OI and the underlying HIV infection. Whilst there are limited data with which to provide definitive guidance on when to start HAART in patients with OIs, these guidelines support early initiation of HAART and provide practical information regarding co-prescribing and management of common complications.

1.2 The patient pathway

The clinical care of patients with known or suspected OIs requires a multidisciplinary approach, drawing on the skills and experience of all healthcare professional groups. Moreover, these guidelines emphasize that inpatients with HIV-related disease often need rapid access to a variety of diagnostic tests and radiological interventions that may not be immediately available at local hospitals. Furthermore, expert interpretation of these tests by supporting specialties such as radiology, histopathology, microbiology and virology is often required. Optimal care of opportunistic infection can only be achieved by the close cooperation of these healthcare professionals and unless all are intimately involved in the care of patients, it is likely that the outcome will be less favourable. In keeping with BHIVA standards for HIV clinical care, patients needing inpatient care for HIV-related disease should ordinarily be admitted to an HIV centre or the relevant tertiary service in liaison with the HIV centre.

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2 Central nervous system opportunistic infections

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Keywords: central nervous system opportunistic infections, toxoplasmosis, *Cryptococcus neoformans*, progressive multifocal leukoencephalopathy, cytomegalovirus (CMV)

2.1 Methods

The PubMed database was searched under the following heading: HIV or AIDS and central nervous system infection or space-occupying lesion or meningitis or encephalitis or pneumonitis and/or *Cryptococcus neoformans*, cryptococcosis, *Toxoplasma gondii*, toxoplasmosis, progressive multifocal leukoencephalopathy, cytomegalovirus or CMV.

2.2 Introduction

Disease of the central nervous system (CNS) is common in HIV. It may be a direct consequence of HIV infection or an indirect result of CD4 cell depletion. Presentation may be predominantly manifested as a space-occupying lesion(s), encephalitis, meningitis, myelitis, spinal root disease or neuropathy (Table 2.1), and may occur in isolation or together with other HIV-related disease. This section deals with cerebral toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML), and cytomegalovirus (CMV) encephalitis and polyradiculitis (Table 2.2 and Fig. 2.1). Mycobacterial disease and primary CNS lymphoma (PCNSL) are not discussed in this section as *Mycobacterium tuberculosis* is the focus of separate guidelines [1] and PCNSL is discussed within the BHIVA Malignancy Guidelines [2].

2.3 General overview

Opportunistic infections of the CNS carry a great risk of morbidity and mortality. Several factors influence the likelihood of a specific aetiology, including CD4 cell count, ethnicity, age, risk group, prophylactic history and geographical location. Clinical evaluation and imaging, often with spinal fluid evaluation, is essential in determining the aetiology and appropriate management. In particular, MR scanning and CSF nucleic acid amplification have refined the approach to diagnostic confirmation so that brain biopsy is less often required (e.g. PML). With the exception of cryptococcal meningitis, therapy is usually commenced without prior confirmation and for toxoplasmosis facilitates distinction of *Toxoplasma* encephalitis from primary CNS lymphoma with confidence, where imaging is nondiagnostic. Early introduction of HAART is also vital in reducing morbidity and mortality, and indeed for PML is the only form of treatment.

Table 2.1 Differential diagnosis of HIV-related opportunistic infections and malignancies of the CNS

Presentation	Main causes
Space-occupying lesion(s)	Toxoplasmosis, primary CNS lymphoma, PML*, TB, cryptococcus, metastatic non-Hodgkin lymphoma (NHL), syphilitic gummae
Encephalitis	HIV, varicella zoster virus, herpes simplex, syphilis
Meningitis	HIV seroconversion, *Cryptococcus*, TB, syphilis, bacteria e.g. *Streptococcus pneumoniae*
Spastic paraparesis	HIV-vacuolar myelopathy, transverse myelitis from varicella-zoster virus, herpes simplex, HTLV-1, toxoplasmosis or syphilis
Polyradiculitis	CMV, NHL

*May also present with focal non-space-occupying lesions.

2.4 *Cryptococcus neoformans*

2.4.1 Background and epidemiology

Cryptococcosis is the commonest systemic fungal infection associated with immunosuppression secondary to HIV infection [3]. Prior to the availability of highly active antiretroviral therapy (HAART) cryptococcosis occurred in approximately 5–10% of individuals infected with HIV [3], although this was higher in certain areas of the world [4,5]. Since the advent of HAART the incidence of cryptococcal disease has dramatically reduced [6,7]. Cryptococcus is an encapsulated yeast ubiquitous in the environment. Epidemiological studies have confirmed the theory that primary infections occur during childhood and are usually asymptomatic [8]. The organism most commonly associated with HIV-related cryptococcal disease in the UK is *C. neoformans* var. *grubii* (serotype A) while *C. neoformans* var. *neoformans* (serotype D) is the second major strain in HIV-seropositive individuals [9]. Symptomatic disease with another subtype, *Cryptococcus neoformans* var. *gattii* (serotype B/C), is also well described in HIV patients [10]. Other subtypes of Cryptococcus have also been rarely described to cause disease [11]. *C. neoformans* var. *neoformans* has been found in association with bird (primarily pigeon) droppings, although nonavian sources are also found [12]. *C. neoformans* var. *gattii* has been isolated from

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Table 2.2 Treatment, maintenance and prophylaxis: recommended first-line drugs and alternatives

	Recommended	Alternative
Cerebral toxoplasmosis	**Induction:** Sulphadiazine Oral therapy (1–2 g qds or15 mg/kg qds) with pyrimethamine (loading dose 200 mg then 50–75 mg daily depending on weight) and folinic acid (10–15 mg daily). Duration 6 weeks. **Maintenance:** Sulphadiazine (500 mg^{-1} g qds) with pyrimethamine (25 mg daily) and folinic acid (10 mg daily). Sulphadiazine may also be given 1–2 g bd **Primary prophylaxis:** TMP-SMX (480–960 mg daily). HAART commencement/optimization.	**Induction:** Clindamycin (600 mg qds iv/oral) with pyrimethamine (loading dose 200 mg then 50–75 mg daily depending on weight) and folinic acid (10–15 mg daily). Further alternatives given in text. **Maintenance**: Clindamycin (300 mg qds or 600 mg tds) with pyrimethamine (25 mg daily) and folinic acid (10 mg daily). **Primary prophylaxis:** Dapsone (50 mg daily) with pyrimethamine (50 mg/weekly) and folinic acid (15 mg/weekly).
Progressive multifocal leukoencephalopathy **Cryptococcal meningitis**	**Induction**: Liposomal amphotericin B (4 mg/kg/day) and 5-flucytosine (100 mg/kg/day). Duration 2 weeks. **Maintenance**: Fluconazole (400 mg daily). Duration 8 weeks. **Secondary prophylaxis:** Fluconazole (200 mg daily). **Primary prophylaxis:** Not indicated.	**Induction:** Fluconazole (iv/oral 400 mg daily) and flucytosine (iv/oral 100–150 mg/kg/day). Itraconazole (iv/oral 400 mg daily) – alternative but less effective. Voriconazole or posaconazole are less studied options. **Maintenance:** Liposomal amphotericin (4 mg/kg/weekly). Itraconazole(200 mg/od) **Secondary prophylaxis:** Itraconazole (200 mg od) or liposomal amphotericin (4 mg/kg/weekly).
CMV encephalitis and radiculopathy	**Induction**: IV ganciclovir (5 mg/kg bd). Duration 3 weeks). **Maintenance**: IV ganciclovir (5 mg/kg daily) or oral valganciclovir (900 mg daily). **Primary prophylaxis:** Not indicated.	**Induction:** Foscarnet (90 mg/kg bd) or cidofovir (5 mg/kg weekly). Duration 2 weeks). **Maintenance:** Foscarnet (90 mg/kg daily) or cidofovir (5 mg/kg fortnightly).

eucalyptus trees [13]. Infections caused with *C. neoformans* var. *gattii* occur mainly in tropical and subtropical regions. Infection with *Cryptococcus* spp. is by inhalation of the organism [14] and localized disease in the lung may occur. Without therapy the yeast rapidly spreads to the blood and is neurotropic, leading to the development of cryptococcal meningitis [15,16]. The progression from cryptococcaemia to meningitis is rapid [17]. Other sites of disease after dissemination may include the skin, where appearances resemble molluscum, and the lung. The prostate gland acts as a sanctuary site for *Cryptococcus* spp. in the immunosuppressed [18].

2.4.2 Presentation

The presenting symptoms are dependent upon the site of infection. Cryptococcal meningitis is the commonest presentation of cryptococcal disease. The commonest symptoms are headache and fever. The incidence of meningism is variable [17,19]. Raised intracranial pressure may be associated with nausea, vomiting, confusion and coma. Cryptococcal meningitis may also be associated with respiratory symptoms from pulmonary disease or with skin lesions such as papules or umbilicated molluscum-like skin lesions.

Pulmonary disease may also occur in the absence of neurological disease. However, isolated pulmonary disease due to cryptococcal infection is unusual in HIV disease [20]. Individuals present nonspecifically with fever and cough with or without sputum and shortness of breath. Chest radiograph appearances are variable but include widespread infiltration, nodular disease, isolated abscess formation and pleural effusion [21–23]. Occasional individuals present with haematological spread without meningitis or overt pulmonary disease. Presentation is with fever, night sweats and occasionally rigors. Rare manifestations of cryptococcal disease include ocular palsy, papilloedema, chorioretinitis and osteolytic bone lesions.

2.4.3 Diagnosis

- All individuals with a positive serum cryptococcal antigen should have a lumbar puncture performed (category III recommendation).
- A positive CSF cryptococcal antigen is the most sensitive diagnostic test for cryptococcal meningitis (category III recommendation).
- All patients undergoing a CSF examination for suspected cryptococcal meningitis should have manometry performed (category III recommendation).

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Fig. 2.1 Management of HIV patients presenting with focal neurology and CD4 count <200 cells/μL.

Notes

(1) *MRI preferred as more sensitive

(2) If there are signs of raised ICP, treat with dexamethasone 4 mg qds initially. Once the patient is stable, gradually tail off. Improvement on steroids maybe due to reduction of cerebral oedema or partial response of lymphoma to corticosteroids

(3) At least 2 weeks maybe necessary to assess for a response to antitoxoplasmal therapy. In some cases, if no urgency, monitor for 4 weeks with repeat MRI.

All HIV patients presenting with a CD4 count less than 200 cells/μL and symptoms compatible with cryptococcosis should have this disease excluded. The principle diagnostic test for disseminated cryptococcal disease is serum cryptococcal antigen, which most commonly uses the latex agglutination method. A negative test generally excludes disseminated cryptococcal disease although there are isolated reports of a negative cryptococcal antigen with disseminated disease [24,25]. False positive cryptococcal antigen may occur in the presence of rheumatoid factor, heterophile antibodies, anti-idiotypic antibodies and *Trichosporon asahii* (*beigelii*) infection [26–28]. Serum cryptococcal antigen may be negative in isolated pulmonary disease [29] and microscopy and fungal culture of respiratory specimens are required to make the diagnosis. All patients with a positive serum cryptococcal antigen

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should undergo further evaluation by lumbar puncture after CT or MRI cerebral scanning. Manometry must always be performed to exclude a raised intracranial pressure. A positive CSF cryptococcal antigen, Indian ink stain of CSF, or CSF cryptococcus culture confirms meningitis. CSF should always be sent for fungal culture. Blood culture should always be performed. Where blood cultures or CSF cultures are positive, isolates may be sent for fungal susceptibility testing where facilities exist [30] Strains with increased azole minimum inhibitory concentrations (MICs) have been reported, in particular from sub-Saharan Africa. However, the correlation between clinical response and fluconazole MIC has been variable [31,32]. Although fungal susceptibilities should be requested initially, the decision to switch therapy should not be based on the antifungal MIC alone but requires supportive laboratory or clinical markers of an impaired response to therapy (category IV recommendation). Poor prognostic factors are blood culture positivity, low white blood cell in CSF (< 20 cells/mL), high CSF cryptococcal antigen (> 1:1024), a confused state and a raised intracranial pressure [33].

2.4.4 Treatment

2.4.4.1 Induction

- Standard induction therapy of cryptococcal meningitis is with amphotericin B, usually combined with flucytosine 100 mg/kg/day (category Ib recommendation).
- Liposomal amphotericin B 4 mg/kg/day intravenously is the preferred amphotericin B preparation on the basis of lower nephrotoxicity than conventional preparations (category III recommendation).
- Fluconazole plus flucytosine or the use of voriconazole or posaconazole may be considered where standard regimens fail or are not tolerated (category IV recommendation).

Historically, the standard of care for the treatment of cryptococcal meningitis in HIV-seronegative individuals has been amphotericin B deoxycholate (0.7–1 mg/kg/day) combined with flucytosine (100 mg/kg/day) [34,35]. However, the advantages and disadvantages of the addition of flucytosine to amphotericin B deoxycholate in the HIV setting should be carefully weighed for each individual patient [36–39]. The addition of flucytosine speeds the rate of sterilization of the CSF [36,39] and reduces the incidence of relapse [40] in patients not receiving HAART. However, flucytosine has been associated with enhanced toxicity in some (though not other) studies and has not been shown to impact on early or late mortality [14,36]. In addition, most of the benefits of flucytosine have been observed in patients not receiving HAART. When flucytosine is given, it may be prescribed orally or intravenously. Flucytosine is associated with haematological toxicity and daily blood counts are required with monitoring of flucytosine levels.

Standard amphotericin B is associated with renal toxicity, and where possible should be replaced by liposomal amphotericin B as the first choice agent (category III recommendation). In one study (including a small number of HIV-seropositive individuals) 30% of those receiving amphotericin B deoxycholate developed acute renal failure with significant associated mortality [41]. Further research has demonstrated that liposomal amphotericin B (4 mg/kg) without concomitant flucytosine therapy sterilized the CSF faster than standard amphotericin B and was associated with lower nephrotoxicity but not with any survival advantage [42]. On the basis of the lower incidence of nephrotoxicity, many pharmacy departments have stopped stocking amphotericin B deoxycholate and, on the basis of at least equivalent efficacy and lower nephrotoxicity, liposomal amphotericin B (4 mg/kg/day intravenously) is the preferred amphotericin B preparation when available for the treatment of cryptococcal meningitis.

Alternative therapies to an amphotericin-based regimen are listed in Table 2.2. When amphotericin-based therapy is not tolerated, an alternative is fluconazole (400 mg/day) with or without flucytosine (100–150 mg/kg/day) [33,37,43]. Fluconazole alone is associated with a higher early, but not overall, mortality than amphotericin B [33]. In individuals with good prognostic factors (see above) some physicians may choose to use a fluconazole-containing regimen first-line due to its ease of administration and low toxicity (category IV recommendation). The addition of flucytosine to fluconazole may result in higher rates of sterilization of CSF [43]. Higher doses of fluconazole have also been utilized [44].

Itraconazole (400 mg/day) is less active than fluconazole [40,45] and should only be used if other agents are contraindicated. There are few data on the use of newer azoles such as voriconazole and posaconazole in HIV patients with cryptococcal meningitis, although these drugs have *in vitro* activity [46,47]. There are case reports of refractory cryptococcal meningitis associated with HIV being treated with both voriconazole and posaconazole [47,48]. These agents are expensive and should only be utilized when other agents fail or are not tolerated. Significant drug–drug interactions occur with the azoles and antiretroviral agents and specialist input is required, and often therapeutic drug monitoring of azoles where available, and antiretrovirals may be warranted (see Table 2.3). Caspofungin lacks activity against *Cryptococcus* species [49].

2.4.4.2 Management of raised intracranial pressure

- CSF manometry should be performed on all patients at baseline or if any signs of neurological deterioration

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Table 2.3 Potential CNS opportunistic infection and antiretroviral drug interactions

Drug name	Interaction with antiretroviral	Action required
Antifungals		
Amphotericin	Tenofovir	Caution – increased risk of renal toxicity with concurrent or recent use.
Itraconazole	Ritonavir increases itraconazole exposure	Avoid high doses of itraconazole Caution with boosted PIs – some PI levels increased
	Efavirenz, etravirine and nevirapine reduce itraconazole levels	Consider alternative, or increase dose Monitor clinical effect
	Maraviroc levels increased	Reduce maraviroc dose (150 mg bd)
Voriconazole	Efavirenz levels increased and voriconazole levels reduced	Not recommended to be used together. Seek HIV specialist pharmacist advice
	Etravirine and voriconazole levels are both increased	No dose adjustment required – monitor for toxicity
	Lopinavir/ritonavir reduces voriconazole levels	Not recommended to be used together. Seek HIV specialist pharmacist advice
Fluconazole	Zidovudine levels increased	Caution – monitor for adverse effects
	Nevirapine levels increased	Caution – monitor for adverse effects
Posaconazole	Efavirenz reduces posaconazole levels	Avoid combination unless benefit to patient outweighs risk
	Atazanavir levels increased	Caution – additional monitoring for toxicity (bilirubin levels)
	Other PIs – levels increased	Monitor for potential increase in toxicity
Caspofungin	Efavirenz and nevirapine reduce levels	Increase caspofungin dose to 70 mg od for those <80 kg
Antivirals		
Valganciclovir/ganciclovir	Zidovudine levels increased and valganciclovir/ganciclovir levels reduced (slightly)	Monitor for signs of haematological toxicity
	Didanosine levels increased with both oral valganciclovir, ganciclovir and IV ganciclovir	Monitor
	Tenofovir	Caution – monitor for signs of increased renal toxicity with concurrent or recent use of valganciclovir/ganciclovir
Foscarnet	Tenofovir	Caution – monitor for signs of increased renal toxicity with concurrent or recent use of foscarnet
Cidofovir	Zidovudine levels increased	Monitor for signs of zidovudine toxicity Consider potential interaction with probenecid which is coadministered with cidofovir
	Tenofovir	Caution – monitor for signs of increased renal toxicity with concurrent or recent use of cidofovir

Antiretroviral drugs, especially the NNRTIs and boosted PIs, have several important drug–drug interactions. This table lists some examples of drug–drug interactions with antiretroviral agents and drugs used in treatment of CNS infections. As the azole antifungal compounds are metabolized via the cytochrome P450 enzyme system they are likely to interact with both NNRTIs and PIs. There are few published data on potential drug interactions with the new antifungal agents. As data and advice changes frequently, this information should always be interpreted in conjunction with the manufacturer's information (www.medicines.org.uk). Other useful web-based reference sources include the Liverpool HIV drug information website (www.hiv-druginteractions.org) and the Toronto Clinic (www.hivclinic.ca/main/drugs_interact.html).

occur, and serial lumbar punctures or neurosurgical procedures are indicated for individuals with an opening pressure >250 mmH_2O (category III recommendation).

Manometry is essential at diagnostic lumbar puncture as there is a significant incidence of raised intracranial pressure associated with cryptococcal meningitis. If the opening pressure is greater than 250 mmH_2O then this should be reduced to below 200 mmH_2O or to 50% of the initial pressure. Lumbar punctures should be repeated daily until stable. Repeat lumbar puncture should always be considered in any patient with cryptococcal meningitis who deteriorates or develops new neurological signs. Resistant cases of raised intracranial pressure may require neurosurgical referral for ventriculo-peritoneal shunt.

Corticosteroids and acetazolamide have not been shown to be of benefit [50,51].

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2.4.4.3 Maintenance

- The preferred maintenance regimen is fluconazole 400 mg once a day orally, started after approximately two weeks of induction therapy (category Ib recommendation).
- The fluconazole dose is then reduced to 200 mg once a day after 10 weeks (category III recommendation).
- A lumbar puncture at two weeks and extension of induction therapy until CSF cultures are negative can be considered in select individuals with poor prognosis at baseline or a poor initial clinical response to induction therapy (category IV recommendation).

Maintenance therapy is essential following induction therapy for all individuals developing cryptococcal disease. In one placebo-controlled study of maintenance therapy following successful induction therapy over one-third of patients relapsed whilst receiving placebo [52].

The timing of switching from induction to maintenance therapy is unclear. Some physicians wish to achieve sterilization of CSF, since CSF cryptococcal burden correlates with risk of relapse and mortality [53]. To achieve this, they continue induction therapy until CSF cultures are negative. Others will give a fixed course of therapy, most often two weeks, and switch the patient to a maintenance regimen, if well, without further lumbar puncture. This may be the preferred option for most individuals, bearing in mind that, assuming HAART is started, the risk of relapse and mortality is likely to be lower than that reported in older studies. There should be consideration of a lumbar puncture and extension of therapy in individuals whose initial poor prognostic factors or slow response to therapy raise concerns that they are less likely to be cured by only two weeks' induction (category IV recommendation).

Options for maintenance therapy are daily fluconazole or itraconazole, or weekly liposomal amphotericin B. Fluconazole has been shown to be superior to amphotericin B with less drug-associated toxicity and lower rates of relapse [54], and also to itraconazole which was associated with higher rates of CSF culture-positive relapse [40]. The optimal dose of fluconazole as maintenance therapy remains unclear. Although the standard dose is 200 mg daily, one retrospective study showed a benefit to a higher dose of 400 mg daily with a lower rate of relapse [55]. Serum cryptococcal antigen measurement is not useful in monitoring for relapse of disease [56].

2.4.4.4 Cryptococcal infection without CNS involvement. Pulmonary cryptococcal infection, isolated cryptococcaemia or cryptococcal disease at another site outside the CNS and lungs should be assessed for associated occult CNS infection by performing an LP. If this is present, treatment is as for meningitis. If CSF examination is negative, isolated pulmonary disease can be treated with fluconazole. There are no controlled clinical studies of the treatment of isolated pulmonary cryptococcal disease in either the HIV or the non-HIV setting. All HIV patients with isolated pulmonary disease should be treated due to the almost certain risk of dissemination. In those with moderate symptoms the treatment of choice is fluconazole 400 mg daily followed by secondary prophylaxis [57,58]. In those with more severe disease, liposomal amphotericin B should be used [57,59] until symptoms are controlled; again this should be followed by secondary prophylaxis. Similarly, in patients with isolated cryptococcaemia there are no studies to guide treatment options. Due to the rapid progression to meningitis from this condition [17] patients should be treated with either fluconazole 400 mg daily if mild or moderately symptomatic or liposomal amphotericin B if symptoms are more severe.

2.4.5 Prophylaxis

- Routine prophylaxis for cryptococcal disease is not recommended (category IV recommendation).

Studies have shown a benefit in reducing the incidence of cryptococcal disease with primary prophylaxis with both itraconazole and fluconazole; however, neither intervention had an effect on survival [60]. There is a risk of the development of resistance and due to this factor and the high cost associated with azole prophylaxis, this approach cannot be recommended.

2.4.6 Impact of HAART

- All individuals diagnosed with cryptococcal disease should receive HAART (category IIb recommendation), which should be commenced at approximately two weeks, after commencement of cryptococcal treatment, when induction therapy has been completed.

The incidence of cryptococcal disease has decreased post-HAART [61]. All individuals should receive HAART (category IIb recommendation), which should be commenced at approximately two weeks, after commencement of cryptococcal treatment, when induction therapy has been completed (category III recommendation). The optimal time to start HAART in patients with cryptococcal meningitis is not known. Physicians have to balance the risk of HIV progression against the hazards of starting HAART, which include toxicities, side effects, immune reconstitution inflammatory syndrome (IRIS) and drug interactions. An increase in mortality has been observed in patients who were initiated on antiretroviral therapy within 72 h of starting treatment for cryptococcal meningitis. This study was performed in Africa, with a small number of patients and may not be relevant to a resource-rich area [62].

Physicians should be aware of the risk of development of IRIS, which is well described with cryptococcal disease

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[63,64]. Common manifestations include aseptic meningitis, raised intracranial pressure, space-occupying lesions in the brain, pulmonary infiltrates or cavities, lymphadenopathy and hypercalcaemia. As with other forms of IRIS, treatment is with continued HAART, if at all possible, and if active infection is excluded consideration of steroids or other anti-inflammatory treatment [65].

One prospective multicentre randomized study suggests secondary prophylaxis for cryptococcal meningitis can be discontinued once the CD4 count is >100 cells/μL in the presence of an undetectable viral load for at least 3 months [66] and small prospective nonrandomized series also support this approach [67–69].

2.5 *Toxoplasma gondii*

2.5.1 Background and epidemiology

Toxoplasma abscesses are the commonest cause of mass lesions in the immunocompromised HIV-seropositive individual world-wide, including sub-Saharan Africa [70]. *Toxoplasma gondii* is an obligate intracellular protozoan whose definite hosts are members of the cat family, as the parasite can complete its sexual cycle only in the feline intestinal tract. Humans acquire the infection by eating animals with disseminated infection or by ingestion of oocytes shed in cat faeces that have contaminated soil, fruits, vegetables and water [71]. The primary infection, in immunocompetent patients, is often asymptomatic but some individuals may develop a mononucleosis-like syndrome. In immunodeficient patients, toxoplasmosis is usually caused by the reactivation of chronic infection acquired earlier in life [72]. Toxoplasma abscesses are the commonest cause of focal mass lesions in the brains of patients with HIV infection and a CD4 T-cell count <200 cells/μL. Seropositivity for toxoplasma varies world-wide and depends on age, dietary habits and proximity to cats; in the UK and US, seroprevalence rates are10–40%, whereas in France rates of 90% reflect differing dietary habits [71]. The lifetime risk of an untreated HIV-seropositive individual who is IgG seropositive for *T. gondii* developing toxoplasma encephalitis is around 25% [72]. However, in one study, 16% of patients with toxoplasmosis diagnosed by biopsy or a successful response to treatment were reported to be seronegative either as a result of primary infection or the loss of seropositivity consequent upon impaired humoral immunity [73]. It is useful to document any patient's toxoplasma serology at first diagnosis of HIV.

2.5.2 Presentation

The clinical presentation with cerebral abscesses evolves over a period of days to weeks with the development of focal neurological signs and symptoms and sometimes seizures. As a result of raised intracranial pressure patients may develop headache and vomiting. Focal signs include hemiparesis or hemisensory loss, visual field deficits, dysphasia, a cerebellar syndrome and a variety of movement disorders as toxoplasma abscesses have a predilection for the basal ganglia. Some individuals present with signs of a diffuse encephalitis with confusion, seizures and altered levels of consciousness. This may progress rapidly to coma and death. Rarely, toxoplasma infection may present as toxoplasma myelitis. The spinal cord may be involved with a transverse myelitis, cauda equina syndrome or with contrast-enhancing intramedullary mass lesions. Presentations outside the nervous system include chorioretinitis and pneumonia.

2.5.3 Diagnosis

- Radiological imaging aids diagnosis. MRI is preferable to CT (category III recommendation).
- Single photon emission computed tomography (SPECT) may also be helpful in excluding the possibility of PCNSL (category III recommendation).
- If there is not a contraindication to lumbar puncture a positive CSF PCR for *T. gondii* helps establish a diagnosis but has only moderate sensitivity (category III recommendation).

The differential diagnosis of toxoplasma abscesses includes PCNSL, tuberculous abscesses and PML. MRI is more sensitive at establishing a diagnosis [74], in particular in detecting lesions in the posterior fossa [75]. If there is a delay in obtaining an MRI, CT should be performed first with MRI later. Typically, the abscesses are multiple ring enhancing lesions at the grey–white interface and in the deep grey matter of the basal ganglia or thalamus [76]. They are associated with cerebral oedema and mass effect. Low CD4 cell counts may be associated with an absence of ring enhancement [75]. Patients with PCNSL cannot be reliably separated from toxoplasma encephalitis by CT/MRI although, when present, lesions that are single, have a periventricular location or demonstrate sub-ependymal spread are suggestive of PCNSL [77]. The lesions found in PML tend to involve mainly white matter, are rarely contrast enhancing and do not exhibit mass effect [75].

SPECT helps to distinguish between infections including abscess and PCNSL, since PCNSL reveal high uptake [78]. Toxoplasma serology is not particularly helpful in the diagnosis [77]. The presence of IgG is only evidence of previous infection. Rising IgG titres would be indicative of reactivation. However, this often does not occur in the immunocompromised patient. Positive serology therefore only indicates that a patient is at risk of developing toxoplasmosis.

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In patients presenting with mass lesions, lumbar puncture is often contraindicated due to raised intracranial pressure. If there is no evidence of mass effect, and there is diagnostic uncertainty, CSF examination maybe helpful. Discussion with the neurosurgical team and an experienced neuroradiologist may be necessary. PCR testing for *T. gondii* on the CSF has a sensitivity of 50% with a specificity of >94% [79–81].

2.5.4 Treatment

- First line therapy for toxoplasma encephalitis is with pyrimethamine, sulphadiazine, folinic acid for 6 weeks followed by maintenance therapy (category Ib recommendation).
- For patients allergic to or intolerant of sulphadiazine, clindamycin is the preferred alternative agent (category Ib recommendation).
- Alternative therapies include trimethoprim-sulphamethoxazole alone (TMP-SMX, co-trimoxazole), atovaquone combined with sulphadiazine or pyrimethamine, but there is limited experience with these (category III recommendations).
- Lack of response to two weeks of treatment, clinical deterioration or features that are not typical of toxoplasma encephalitis should lead to consideration of a brain biopsy (category IV recommendation).

With increasing experience it is now standard practice to treat any HIV patient with a CD4 count of <200 cells/μL and a brain mass lesion with anti-toxoplasma therapy. Patients should be screened for G6PDH deficiency as this is highly prevalent in individuals originating from Africa, Asia, Oceania and Southern Europe. However, sulphadiazine has been found not to be haemolytic in many G6PDH-deficient individuals although any drop in haemoglobin during therapy should prompt testing. Antimicrobial therapy is effective in toxoplasmosis with 90% of patients showing a response clinically and radiologically within 2 weeks [82]. A response to treatment is good evidence of diagnosis without having to resort to more invasive procedures. Regimens that include sulphadiazine or clindamycin combined with pyrimethamine and folinic acid show efficacy in the treatment of toxoplasma encephalitis [82–84]. In a randomized clinical trial, both showed comparable efficacy in the acute phase of treatment, although there was a trend towards less response clinically in the group receiving the clindamycin-containing regimen and significantly more side effects in the sulphadiazine-containing regimen [84]. In the maintenance phase of treatment there was an approximately two-fold increase in the risk of progression in the group who received the clindamycin-containing regimen. On this basis the sulphadiazine-containing regimen is the preferred regimen with the clindamycin-containing regimen reserved for those who are intolerant of sulphadiazine.

For acute therapy, because of poor absorption, a loading dose of 200 mg of pyrimethamine followed by 50 mg/day (<60 kg) to 75 mg/day (>60 kg) should be given together with folinic acid 15 mg/day (to counteract the myelosuppressive effects of pyrimethamine) and either sulphadiazine 1–2 g qds, although consideration should be given to weight based dosing with 15 mg/kg qds or clindamycin 600 mg qds. Sulphadiazine and clindamycin have good bioavailability so the oral route is preferred. Some studies show that sulphadiazine can be given. The intravenous form of sulphadiazine is not currently available within the United Kingdom. In the unconscious patient, a nasogastric tube may be necessary to give pyrimethamine as it is also not available as an intravenous preparation. Clindamycin can also be given intravenously. If a patient develops a rash, usually generalized and maculopapular, this is most likely to be the sulphadiazine or clindamycin component. The offending drug should be stopped and switched if possible to the other. Sulpha desensitization can be undertaken but this is a complicated and lengthy process.

After initial acute therapy for 6 weeks, patients require switching to maintenance therapy (secondary prophylaxis). This involves using the same drugs but in lower doses: pyrimethamine 25 mg/day plus sulphadiazine 500 mg^{-1} g qds or 1–2 g bd or clindamycin 300 mg qds or 600 mg tid with supplemental folinic acid 15 mg/day. Although sulphadiazine has traditionally been administered four times a day more recent pharmacokinetic data suggests bd dosing may be as effective and could be used for maintenance therapy [85]. There is, however, to our knowledge no direct comparison of bd and qid dosing although the bd regimen has been compared to a thrice-weekly maintenance regimen of sulphadiazine and pyrimethamine [86]. There is limited experience to guide therapy if sulphadiazine or clindamycin-containing regimens cannot be tolerated. Possible alternatives include: pyrimethamine and folinic acid (doses as above for acute therapy) with atovaquone (1500 mg bd) [87]; sulphadiazine (doses as above for acute therapy) plus atovaquone (1500 mg bd) [87]; pyrimethamine and folinic acid (doses as above for acute therapy) with either azithromycin, clarithromycin, doxycycline or dapsone; and trimethoprim 10 mg/kg/day and sulphamethoxazole 50 mg/kg/day tds or qds orally or IV [88,89]. To date, these alternative regimens have not been shown to be as effective as the first-line options but intravenously administered trimethoprim-sulphamethoxazole is a useful option when an oral formulation cannot be used in an unconscious patient.

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Corticosteroids should not be used routinely as they cloud the diagnostic therapeutic trial. They are indicated in patients with symptoms and signs of raised intracranial pressure such as headache, vomiting, drowsiness and papilloedema. When indicated dexamethasone 4 mg qds, gradually reducing, is the treatment of choice. However, any response clinically and radiologically may be due to a reduction in cerebral oedema rather than a response to the anti-toxoplasma therapy. Clinical deterioration after tapering the steroids merits consideration of a diagnostic brain biopsy. Brain biopsy should be considered when there is (1) failure of response to at least two weeks of anti-toxoplasma therapy; (2) clinical deterioration while on therapy; (3) a single, especially periventricular, lesion on MRI; or (4) a mass lesion(s) if the CD4 count is above 200 cells/μL. If a patient presents with or develops seizures (25–30%), antiepileptic medication is necessary. However, there is no evidence to support the routine prescribing of antiepileptic drugs in patients with toxoplasmosis.

2.5.5 Prophylaxis

- HIV patients with a CD4 count of <200 cells/μL and positive toxoplasma serology require prophylaxis against toxoplasma encephalitis (category IIb recommendation).

Although there are no randomized clinical trials of toxoplasma prophylaxis *per se*, trials of PCP prophylaxis have demonstrated efficacy of TMP-SMX and dapsone plus pyrimethamine against toxoplasma encephalitis [90,91]. Various doses can be used but TMP-SMX 480–960 mg/day is the preferred regimen. Dapsone 50 mg/day and weekly pyrimethamine 50 mg is reserved for individuals who are allergic to TMP-SMX. Atovaquone may also be considered. In addition, all HIV-seropositive individuals should be advised to avoid the ingestion of undercooked red meat, to wash their hands after any contact with soil, and to avoid emptying cat litter trays. If this is not feasible, emptying cat litter trays daily and ensuring that hands are washed after all disposal of cat excreta must be advised.

2.5.6 Impact of HAART

- Primary and secondary prophylaxis can be discontinued when the CD4 count is repeatedly above 200 cells/μL (level Ib recommendation).

HAART has lessened the incidence of toxoplasma encephalitis. HAART has been associated with a decline in toxoplasma encephalitis and should be initiated as soon as the patient is clinically stable (usually approximately 2 weeks after commencing acute treatment of toxoplasma encephalitis to lessen the likelihood of IRIS). There have been a number of reports of IRIS associated with toxoplasma encephalitis [92]. After the initiation of HAART, primary prophylaxis maybe discontinued after successful suppression of HIV viral replication and restoration of the CD4 counts to >200 cells/μL for 3 months [93]. After HAART, maintenance therapy may be discontinued after 6 months of successful suppression of HIV viral replication and elevation of CD4 count to >200 cells/μL [69,94,95].

2.6 Progressive multifocal leukoencephalopathy (PML)

2.6.1 Background and epidemiology

First identified as a clinical entity in 1958, progressive multifocal leukoencephalopathy (PML) was subsequently characterised to be an opportunistic infection (OI) in 1971 when virus particles were identified from a patient with underlying Hodgkin disease (named JC virus after the patient initials). This was later further identified as being a double-stranded DNA 40-nm icosahedron virus belonging to the subfamily of Polyoma viruses.

Asymptomatic seroconversion occurs predominantly in childhood although seroprevalence continues to increase until old age and over 70% of the population are seropositive [96]. The exact mechanism of transmission is ill-understood but is probably by respiratory secretions and via the tonsillar tissues. Following primary infection, the virus disseminates and sets up latent infection in several organs (spleen, bone marrow, kidneys and B-lymphocytes). With subsequent immune suppression, JC virus productively replicates and is transported to the brain by B-lymphocytes where it infects permissive oligodendrocytes via the serotonin receptor [97].

The advent of HIV radically changed the epidemiology from what was an exceptionally rare complication of patients with reticuloendothelial disease or immunosuppressed following organ transplantation, to an OI identified in up to 5% of patients with AIDS with limited reduction after introduction of HAART and no change in the high mortality rate [98,99]. PML caused approximately 20% of focal brain lesions pre-HAART [100].

2.6.2 Presentation

The cardinal pathological feature and underlying process determining the clinical presentation is demyelination of white matter, which is irreversible. Classic PML presents as a subacute illness without constitutional symptoms in patients with severe immunodeficiency. Progressive focal neurology, mainly motor deficit, altered mental or mood status, ataxia or cortical visual symptoms, develop over weeks to months. The presence of the focal features helps distinguish the cognitive syndrome associated with PML from HIV encephalopathy. Seizures may rarely occur. Rare but increasingly recognized PML may present after the introduction of ARV treatment and reflects an immune reconstitution phenomenon [101].

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2.6.3 Diagnosis

- MRI appearances and JC virus detection by PCR in a CSF sample are sufficient to make a diagnosis in most cases and avoid the need for a brain biopsy (level III recommendation).

Early diagnosis is paramount. Brain biopsy has long been regarded as the gold standard with a sensitivity of 64–96% and a specificity of 100%. With imaging refinements, MRI combined with CSF DNA amplification has allowed avoidance of biopsy. Lesions are usually bilateral, asymmetric, non-enhancing T2 hyperintense T1 hypointense, restricted to white matter and with no oedema. The asymmetric nature and sharp demarcation helps differentiate from HIV encephalopathy. In the context of antiretroviral treatment, features may be atypical. Pre-HAART, JC DNA in the CSF detected by PCR had sensitivity of 72–92% and a specificity of 92–100%. However, since the introduction of HAART sensitivity has fallen to approximately 50% reflecting reduced viral replication and increased clearance of virus from the CSF [102,103].

Factors associated with a poor prognosis include clinical (older age, brainstem involvement, lowered level of consciousness), viral (high CSF JC viral load with delayed clearance with HAART), radiological (early brainstem involvement), and immunological (CD4 count <100 cells/μL) [104]. Evidence of immunological responsiveness, higher CD4 cell counts, contrast enhancement on imaging, perivascular mononuclear infiltrates and JC-specific cytotoxic T lymphocytes are associated with improved prognosis.

2.6.4 Treatment

- HAART is the only intervention that has improved clinical outcomes with PML (category III recommendation).

Although cidofovir and cytarabine (ARA-C) are active against non-human Polyoma virus and JC virus *in vitro*, respectively, with identifiable reduction in CSF JC viral load *in vivo*, neither drug has been shown to arrest the disease process and there remains no specific treatment for PML other than commencing or optimizing ARV treatment. Cidofovir was shown in a large multicentre study to provide no additional benefit to HAART alone [105] and these results have been confirmed in retrospective analyses of pooled data from prior cohort or observational studies [106,107]. Similarly, cytarabine, either intravenously or intrathecally, failed to demonstrate additional benefit to ARV treatment, albeit this study was conducted pre-HAART [108]. Hence, HAART remains the only therapeutic option. The choice of HAART should consider probable CNS penetration as one study has shown a better outcome with drugs based on their CNS penetration score [110].

2.6.5 Prophylaxis

There is no therapy that has been identified as effective in preventing PML.

2.6.6 Impact of HAART

From a predicted survival of 10% at one year, 50% of patients receiving HAART now survive for this length of time [110] and some patients enter true remission of disease with stabilization of neurological morbidity and the development of atrophy and gliosis on MRI. Also, since the impact of HAART on PML may be less than for other focal neurological lesions, the relative contribution of PML to the incidence of focal lesions in the brain may have increased [100].

2.7 Cytomegalovirus (CMV)

2.7.1 Background and epidemiology

Cytomegalovirus (CMV) is a member of the human β-herpesviruses. Like other members, it has the ability to establish lifelong persistent and latent infection after primary exposure. In the context of immunodeficiency, particularly cell-mediated, this may result in severe primary or reactivated clinical disease.

Nearly all men who have sex with men (MSM) are seropositive whereas in heterosexuals and injection drug users, the rate is 50–75% [111]. With clinical progression of HIV, latent CMV reactivates, leading to viraemia and, in a proportion, end-organ disease. Prior to the advent of HAART, observational studies demonstrated that 20–40% of patients with AIDS developed CMV disease, with many more patients having evidence of disease at post mortem. End-organ disease incidence becomes substantially higher when the CD4 count falls to <50 cells/μL. The major sites of CMV disease are the retina, which accounts for approximately three-quarters of cases, the GI tract, the lung, the liver and biliary tract, the heart, adrenal glands and the nervous system (encephalitis and polyradiculitis). The widespread uptake of HAART has radically altered the epidemiology with most patients starting treatment before they become at risk for CMV disease. Nervous system infection accounts for $<1\%$ of clinical CMV disease [112,113].

2.7.2 Presentation

Clinical signs and symptoms are insensitive and difficult to distinguish from AIDS-dementia complex. A subacute history with progressive disorientation, withdrawal, apathy, cranial nerve palsies, and nystagmus is typical whereas symptoms of depression and mental slowing are more evident in AIDS-dementia complex: the micronodular form is often subclinical or gives rise to more subtle cognitive impairment. CMV encephalitis is typically more

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aggressive than HIV brain disease. Clinical evidence of cerebellar or brainstem involvement is present in 30%: features of polyradiculitis and retinitis (up to 75%) may coexist [114]. Presentation of lumbosacral polyradiculitis is usually as a rapidly progressive, painful, bilateral ascending flaccid paralysis with saddle anaesthesia, areflexia, sphincter dysfunction and urinary retention.

2.7.3 Diagnosis

- MRI scanning and CSF PCR are the preferred diagnostic tests (category III recommendation).

Development of any neurological feature in a patient with HIV with a low CD4 cell count warrants urgent investigation, initially with neuroimaging and, if not contraindicated, lumbar puncture. On CT scan, diffuse white matter hypodensities with ependymal enhancement, ventricular enlargement, meningeal enhancement and focal or nodular ring-enhancing lesions are seen. However, MRI is far more sensitive when these features are best revealed on gadolinium enhanced T1 weighted scans with periventricular enhancement commonly seen. However, imaging lacks sensitivity and many patients have normal or nonspecific changes [115]. CSF examination is rarely grossly abnormal although a slightly raised protein and mild lymphocytosis are not infrequent. In patients with isolated or concomitant polyradiculitis, diffuse enhancement of cord parenchyma, nerve roots and meninges is seen on contrast-enhanced MR and a characteristically pronounced polymorphonuclear cell pleocytosis is usual. Electromyogram studies demonstrate axonal neuropathy and can help distinguish CMV polyradiculitis from an acute inflammatory demyelinating polyneuropathy. Diagnosis of both conditions is based around nucleic acid amplification of CMV DNA. A positive CSF PCR has a sensitivity of $>80\%$ and a specificity of $>90\%$ with negative and positive predictive values of 86–92% and 95–98%, respectively [116–119]. However, PCR may rarely be negative in patients subsequently found to have active CMV disease of the brain. Brain biopsy is rarely indicated in view of localization.

2.7.4 Treatment

- Ganciclovir with or without foscarnet is the treatment of choice (category III recommendation).
- HAART should also be instituted after initial anti-CMV therapy (category III recommendation).

There have been no prospective controlled trials for CMV neurological disease and, although well designed randomized controlled trials on the therapeutic efficacy of ganciclovir, foscarnet, valganciclovir and cidofovir (all effective) exist for CMV retinitis, the results of these cannot be extrapolated to encephalitis or polyradiculitis [119–121]. In a small open noncomparative study in the pre-HAART era, combination treatment with ganciclovir and foscarnet did improve or stabilize encephalitis/polyradiculitis in 74% of 31 HIV-seropositive patients with neurological disease; however, overall mean survival was only 3 months [122]. Similar clinical improvements in CMV polyradiculitis have been found with both drugs individually or together in retrospective cohort analyses [123,124]. Both drugs have also been shown to reduce CSF CMV-DNA load. Correcting the profound immunodeficiency by commencing or optimizing HAART is critical in management although no specific data exist for CMV disease of the nervous system. Optimal duration of treatment for both conditions remains uncertain.

2.7.5 Prophylaxis

- Prophylaxis against CMV encephalitis/polyradiculitis is not required but HAART is likely to decrease the incidence of these conditions (category IV recommendation).

There have been no prospective controlled trials for CMV neurological disease and, although well-designed randomized controlled trials on the prophylactic efficacy of aciclovir (not effective), valaciclovir, ganciclovir, and valganciclovir (all effective) exist for CMV retinitis, the results of these cannot be extrapolated to encephalitis [125–127]. Given that HAART has been demonstrated to reduce the risk of CMV end-organ disease and that this is a complication rarely seen where the CD4 is >50 cells/μL, the key to preventing encephalitis is initiation of ARV drugs according to national and international treatment guidelines [128]. Although good information is available to suggest maintenance therapy can be discontinued for CMV retinitis with immune recovery and a sustained rise in CD4 >100 cells/μL, no such evidence exists for neurological disease and a more cautious approach is advised. This decision should be based upon clinical, CSF and blood CMV-DNA levels, and imaging improvement.

2.7.6 Impact of HAART

HAART decreases the incidence of CMV retinitis and CMV disease in general but specific data for encephalitis do not exist. Although CMV IRIS is reported in other settings, there are limited data on its presentation as a neurological disease at this time.

Abbreviations: PML, progressive multifocal leukoencephalopathy; PCNSL, primary central nervous system lymphoma; NHL, non-Hodgkin's lymphoma; KS, Kaposi's sarcoma; CT, computed tomography; MRI, magnetic resonance imaging; CRAG, cryptococcal antigen; TB, tuberculosis; ICP, intracranial pressure.

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2.8 References

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3 Pulmonary opportunistic infections

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3.1 Methods

The PubMed database was searched under the following headings: HIV or AIDS and lung or pneumonia or pneumonitis and/or *Pneumocystis carinii*, *Pneumocystis jirovecii*, Pneumocystis pneumonia, PCP, *Cryptococcus neoformans*, cryptococci, *Cryptococcus*, *Aspergillus*, aspergillosis, CMV, influenza A virus, influenza B virus, parainfluenza virus, respiratory syncytial virus, bacteria and vaccination.

3.2 Introduction

The immune dysregulation associated with HIV results in an increased incidence of respiratory infection at all CD4 T-cell counts. Early reports of the dramatic increased risk of Pneumocystis pneumonia (PCP) in advanced HIV disease have tended to overshadow the finding that other respiratory pathogens are also more common in HIV disease (Table 3.1). The widespread use of prophylaxis against opportunistic infections together with HAART has reduced the risk of life-threatening infection, though it has not returned to the background levels present in HIV-sero negative populations [1]. Mycobacterial disease is not discussed in this section as *Mycobacterium tuberculosis* is the focus of separate guidelines [2].

3.3 General overview

Pulmonary symptoms may arise from infection with a wide variety of organisms although PCP and bacterial pneumonia predominate. A simple patient risk assessment allows the clinician to determine the likelihood that other opportunistic infections (OI) are the cause of severe respiratory disease and that further pathogens may need to be considered. Relevant factors include: (1) patient use of effective OI prophylaxis or HAART; (2) recent discharge from hospital or current hospital admission >5 days (nosocomial infections); (3) country/place of residence and travel history; (4) history of active injecting drug use, since these individuals are at increased risk of bacterial pneumonia and TB; (5) level of host immunity; (6) neutropenia; and (7) use of prolonged courses of immune modulators (e.g. corticosteroids).

Treatment is often started prior to laboratory confirmation of diagnosis. The intensity with which investigation is undertaken is usually determined by the patient risk assessment, the severity of the illness and the resources available locally.

- While empirical therapy (usually directed against bacterial pathogens) may be appropriate for patients with CD4 counts >200 cells/μL, every effort should be made to confirm a specific diagnosis in the more immunocompromised individual (category IV recommendation).

3.4 *Pneumocystis jirovecii*

3.4.1 Background and epidemiology

Pneumocystis jirovecii is a fungus that causes infection specific to humans [3]. The great majority occur in immunocompromised subjects and are associated with

Table 3.1 Possible causes of severe HIV-related respiratory disease

Bacteria	Fungi	Parasites	Viruses	Non-infectious
Streptococcus pneumoniae	*Pneumocystis jirovecii*	*Toxoplasma gondii*	Cytomegalovirus	**Kaposi's sarcoma**
Haemophilus influenzae	*Cryptococcus neoformans*	*Strongyloides stercoralis*	Adenovirus	**Lymphoma: Hodgkin and non-Hodgkin**
Staphylococcus aureus	*Histoplasma capsulatum*		Influenza A virus	**Lung cancer**
Pseudomonas aeruginosa	*Penicillium marneffei*			**Emphysema**
Escherichia coli	*Aspergillus* spp			**Immune reconstitution inflammatory syndrome**
Mycobacterium tuberculosis	*Coccidioides immitis*			**Pulmonary hypertension**
Mycobacterium avium-intracellulare complex	*Blastomycetes dermatitidis*			**Lymphoid interstitial pneumonitis**
Mycobacterium kansasii				**Non-specific interstitial pneumonitis**
				Sarcoid
				Pulmonary thrombo-embolic disease

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respiratory symptoms [4]. Current evidence suggests that PCP arises by re-infection from an exogenous source [5]. Evidence for nosocomial transmission exists but is limited [5]. Before the advent of preventative therapy and HAART, PCP occurred in up to 80% of HIV-seropositive individuals with AIDS [6]. In the UK this has declined considerably.

Almost 90% of cases occur in HIV-seropositive persons with CD4 T-cell counts <200 cells/μL (or a CD4 T-cell percentage $<14\%$). Other predictive factors for PCP in subjects not receiving effective HAART, include non-adherence to prophylaxis, oral candidiasis, oral hairy leukoplakia, unintentional weight loss, recurrent bacterial pneumonia, previous PCP and a high plasma HIV load [6–12].

3.4.2 Presentation

The typical presentation of PCP is with exertional dyspnoea, which progresses over several weeks, malaise and a dry cough. An inability to take a deep breath and fever are often apparent [13]. Rarer presentations include a more rapid onset, haemoptysis and pleuritic chest pain. Purulent sputum production suggests bacterial infection – although this can be present as a co-pathogen in around one-sixth of cases [14]. Physical examination reveals tachypnoea, normal breath sounds or, less frequently, end-inspiratory crackles. Wheezing and signs of focal consolidation or pleural effusion are less common presentations [13]. Spontaneous or infection-associated pneumothorax in an HIV-seropositive individual should prompt exclusion of PCP [15]. Radiological findings in the chest include perihilar haze, interstitial infiltrates (characteristically sparing the apices and costo-phrenic angles), pneumatocoeles and pneumothoraces. Upper lobe infiltrates alone have been reported to occur in individuals who are receiving inhaled pentamidine prophylaxis. A normal chest radiograph has been reported to occur in up to 39% of patients and should, therefore, not distract from pursuing the diagnosis of PCP if clinically suspected [16,17].

3.4.3 Diagnosis

There are no clinical features specific to PCP. Radiology and nuclear medicine tests are not particularly sensitive or specific [18,19]. Other opportunistic infections may mimic the typical radiological features of PCP [20,21].

Demonstration of a fall in oxygenation between rest and exercise has been validated as a reasonably specific test for PCP in cases with a normal or near-normal chest radiograph who have no previous history of PCP [22], but is not reliable enough to make a diagnosis without confirmatory microbiology. In conclusion, whilst PCP remains a very common AIDS diagnosis in the UK [23] and the clinical and radiological presentation may be classical, neither clinical nor radiological presentation are sufficiently specific and further microbiological investigations are required to confirm PCP and exclude alternative diagnoses or co-pathology.

- It is important to obtain either tissue samples or body fluid in which the organism can be identified (category III recommendation).
- In view of the current reduction in PCP presentations, all cases should undergo investigation and not just receive treatment empirically for presumed PCP (category IV recommendation).

If induced sputum (IS) is routinely available, this can be performed initially (sensitivity 50–90%). If IS results are negative or inconclusive, then the patient should be assessed for bronchoscopy with broncho-alveolar lavage (BAL; diagnostic sensitivity $>90\%$) [24–27]. Some may choose BAL as the first-line investigation employed. Open lung biopsy (diagnostic sensitivity 95–98%) is reserved for the occasional patient, with negative initial tests, and who is not improving on empirical treatment [28,29]. Spontaneously expectorated sputum is not an adequate alveolar sample and should not be processed.

Pneumocystis jirovecii cannot be cultured *in vitro*; diagnosis relies on visualization of the organism using either histochemical (typically with silver stains such as Grocott–Gomori methenamine silver stain) or immunofluorescent stains.

Nucleic acid amplification techniques (NAAT) using a variety of primers have been reported with induced sputum, BAL and oral wash specimens [30–33]. In general NAAT-based tests have increased sensitivity but reduced specificity compared to visualization; and the specificity varies by protocol. In one study comparing two NAAT-based assays the sensitivities were 97–98% but specificities ranged from 68% to 96% [30]. The sensitivity is lower using samples that are obtained from more easily obtained specimens such as sputum or oral washes.

NAAT-based assays, although not widely available, can provide information on the molecular epidemiology of PCP and the frequency of mutations in Pneumocystis' dihydropteroate synthase gene (which is associated with previous exposure to sulpha- drugs – see later).

Currently, no definitive recommendations concerning NAAT-based assays can be made. Where centres use them as part of a diagnostic algorithm they must be interpreted with input from the testing laboratory in the light of their sensitivity and specificity. They should be combined with a definitive visualization technique (category IV recommendation).

Treatment should not be delayed in a presumed case, by having to wait for a diagnostic procedure, as adequate

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pulmonary samples can be obtained up to 7–10 days after starting specific anti-pneumocystis therapy [34].

3.4.4 Treatment

- First-line treatment for moderate–severe PCP [PaO2 $\leq$ 9.3 kPa ($\leq$ 70 mmHg)] is with high-dose intravenous (iv) trimethoprim-sulphamethoxazole for 21 days (co-trimoxazole, TMP-SMX) (category Ib recommendation).
- Some clinicians will continue with iv therapy for the duration; many switch individuals showing a good initial response to oral therapy at doses equivalent to those used for mild–moderate severity disease (category IV recommendation).
- Oral or intravenous corticosteroids should be started in all cases of suspected moderate–severe PCP with a PaO2 < 9.3 kPa (< 70 mmHg) or SpO2 < 92% (category Ib recommendation).
- First-line treatment for mild–moderate disease [PaO2 > 9.3 kPa (> 70 mmHg)] is with oral TMP-SMX (category Ib recommendation).

Co-trimoxazole is a highly effective agent when given for 21 days. It has an efficacy of at least 90% in mild disease and around 70% in more severe cases [35–38]. It has shown similar or better outcomes when compared to iv pentamidine in randomized clinical trials of treatment of PCP [35–37]. Dosing for moderate–severe PCP [PaO2 $\leq$ 9.3 kPa ($\leq$ 70 mmHg), see Table 3.2] is TMP-SMX 120 mg/kg/day iv for 3 days then reduced to 90 mg/kg/day iv for 18 further days [36,37]. In practice the total daily dose may be divided either qid or tid. The intravenous route is preferred for severe disease [39]. For mild–moderate PCP [PaO2 > 9.3 kPa (> 70 mmHg)], dosing is either via the oral route (TMP-SMX 1920 mg tid or 90 mg/kg/day tid) or using the iv regimen described above [40–42]. The dose reduction from 120 mg/kg/day to 90 mg/kg/day, in severe disease, has equivalent efficacy but a lower incidence of adverse events than continuous use of higher-dose therapy [36].

Individuals with a PaO2 < 9.3 kPa (< 70 mmHg) or SpO2 < 92%, should receive prednisolone 40 mg bd po, days 1–5, 40 mg od po, days 6–10, 20 mg od po, days 11–21 [43,44]; or if unable to take oral medications, methylprednisolone at 75% of this dose [45]. The benefit of corticosteroid therapy is documented only where it has been commenced within 72 h of starting specific anti-PCP therapy.

A favourable treatment response may take 7 days or more. The decision to switch from one drug to another is driven by either treatment-limiting toxicity or lack of efficacy.

Sulphamethoxazole inhibits dihydropteroate synthase (DHPS). DHPS mutations have been associated with duration of prior TMP-SMX prophylaxis and also geographical factors, which may influence patient-to-patient transmission [46,47]. Although DHPS mutations may be found in subjects with failure of primary prophylaxis [48] it remains controversial whether these mutations influence the efficacy of treatment with TMP-SMX based regimens. Some early studies reported an association with treatment failure [47,48], while more recent work has not shown this [49–51]. One recent study suggests that the frequency of DHPS mutations may be falling in the HAART era in association with less long-term exposure to PCP prophylaxis [52]. Overall the outcome of PCP is more influenced by the severity of PCP than by the presence of DHPS mutations [49]. There is currently no evidence to support the routine determination of DHPS mutations; or that if they are detected early in treatment, patients should not receive TMP-SMX (category III recommendation).

In many studies salvage treatment is defined as the regimen given after a change of the primary drug regimen on the grounds of suspected treatment failure and occurring after at least 5 days of anti-PCP therapy. It is reported to occur in up to one-third of subjects on treatment [40–42,53,54]. Current evidence suggests that for a given level of PCP severity there is little to choose in terms of efficacy between the different second-line drugs [40–42,53]. The choice of treatment is therefore determined by patient tolerance and ability to take either oral or iv medication. For severe PCP, treatment options are clindamycin 600–900 mg qid/tid iv or 300–450 mg tid/qid po

Table 3.2 Stratification of disease severity in PCP [149]

	Mild	Moderate*	Severe
Symptoms and signs	Dyspnoea on exertion with or without cough and sweats	Dyspnoea on minimal exertion and occasionally at rest; cough and fever with or without sweats	Dyspnoea and tachypnoea at rest; fever and cough
Oxygen PaO_2 room air, at rest in kPa (mmHg)	> 11.0 (> 83)	8.1–11.0 (61–83)	$\leq$ 8.0 ($\leq$ 60)
SaO_2 at rest on air	> 96	91–96	< 91
Chest radiograph	Normal or minor perihilar shadowing	Diffuse interstitial shadowing	Extensive interstitial shadowing with or without diffuse alveolar shadowing

*Note: for treatment purposes moderate severity is grouped with severe disease if $PaO_2 \leq 9.3$kPa or mild disease if $PaO_2 > 9.3$kPa.

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and primaquine 15–30 mg od po or pentamidine 4 mg/kg od iv for 21 days. Many clinicians favour clindamycin-based therapy in view of the toxicity profile of iv pentamidine [38,55]. Good bioavailability allows clindamycin to be given by the oral route unless the patient is unable to take oral medicines. A lower rate of methaemglobinaemia means the 15 mg dose of primaquine is recommended [42].

For mild–moderate disease, trimethoprim 20 mg/kg/day po in divided doses and dapsone 100 mg od po for 21 days or atovaquone liquid suspension 750 mg bid po for 21 days are alternative options if TMP-SMX is not tolerated or the individual is allergic to TMP-SMX [40,41,53,56].

- Glucose 6-phosphate dehydrogenase deficiency (G6PD) levels should be checked prior to TMP-SMX, dapsone or primaquine use (category IV recommendation)

G6PD is classified by the level of red blood cell (RBC) enzyme activity and is common in patients of African origin but also some Mediterranean populations, Sephardic Jews and certain Chinese populations. The level of the G6PD enzyme in RBCs is usually higher in patients of African origin than some of the Mediterranean groups who exhibit more severe levels of G6PD enzyme deficiency. Haemolysis may be triggered by oxidant drugs, which include primaquine and dapsone, but can also occur with sulphamethoxazole when used at the higher doses used during iv treatment of PCP [57–59].

G6PD levels should be checked before (or as soon after starting as possible) administering these agents, but treatment should not be delayed while waiting for the result. As such, it is reasonable to commence first-line treatment with a sulphamethoxazole-containing regimen or if the individual is allergic or intolerant an alternative regimen, pending the result of the G6PD assay. If there is evidence of haemolysis this regimen can then be stopped and an alternative agent, as indicated by disease severity, such as pentamidine or atovaquone (which do not cause oxidant stress in RBCs), may be used if G6PD deficiency is confirmed. If an individual develops haemolysis, is G6PD-deficient or comes from a population at high risk of significant G6PD deficiency, treatment decisions should be taken in consultation with a haematologist.

The overall survival following an episode of PCP approaches 90% [60]. However, a number of individuals will deteriorate and require respiratory support. Early use of continuous positive airway pressure (CPAP) techniques in patients who are hypoxic but not hypercapnic is helpful and may avoid the need for formal mechanical ventilation. It is suggested that early discussion and advice is sought from the ICU for all patients with moderate–severe PCP as many may benefit from close monitoring and advice on initiation of respiratory support. Survival following admission to ICUs experienced in management of severe PCP is now around 40–50% [61] (see 12 Intensive care).

- At a minimum, mechanical ventilation should be undertaken in patients who deteriorate early in treatment, or who have good functional status documented prior to the acute respiratory episode (category III recommendation) [60].

3.4.5 Prophylaxis

- PCP prophylaxis should be used in all HIV-seropositive individuals with a CD4 T-cell count persistently <200 cells/μL, or a CD4 T-cell percentage of all lymphocytes $<14\%$, or oral candidiasis or previous AIDS-defining illness [62] (category Ib recommendation).
- TMP-SMX is the agent of choice. Although other agents may have similar efficacy against PCP, they do not provide the additional protection provided by TMP-SMX against other infections and some are not as effective at low CD4 T-cell counts (category Ib recommendation).

The preferred regimen (see Table 3.3) is TMP-SMX, one double-strength tablet (960 mg TMP-SMX) [63] or one single-strength tablet (480 mg TMP-SMX) once daily. These

Table 3.3 Primary and secondary prophylaxis regimens for *Pneumocystis jirovecii*

Drug	Dose	Notes
Trimethoprim-sulphamethoxazole (co-trimoxazole, TMP-SMX)	One double-strength (TMP-SMX 960 mg) tablet od po or	Other options for primary prophylaxis: one double-strength tablet po three times a week
	One single-strength (TMP-SMX 480 mg) tablet od po	Protects against toxoplasmosis and certain bacteria
Dapsone	50–200 mg od po	With pyrimethamine (50–75 mg po weekly) protects against toxoplasmosis
Pentamidine	300 mg via Respirgard II (jet) nebulizer every 4 weeks	Less effective in subjects with CD4 <100 cells/μL Provides no cross-prophylaxis against other OI Risk of infectious aerosol produced by nebulization Alters presentation of PCP and predisposes to extra-pulmonary pneumocystosis Associated bronchospasm
Atovaquone	750 mg bd po	Absorption increased if administered with food Protects against toxoplasmosis

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Table 3.4 Protocol for co-trimoxazole desensitization among adults and adolescents

Step	Dose
Day 1	80 mg sulphamethoxazole + 16 mg trimethoprim (2 mL oral suspension*)
Day 2	160 mg sulphamethoxazole + 32 mg trimethoprim (4 mL oral suspension*)
Day 3	240 mg sulphamethoxazole + 48 mg trimethoprim (6 mL oral suspension*)
Day 4	320 mg sulphamethoxazole + 64 mg trimethoprim (8 mL oral suspension*)
Day 5	One single-strength sulphamethoxazole-trimethoprim tablet (400 mg sulphamethoxazole + 80 mg trimethoprim)
Day 6 onwards	Two single-strength sulphamethoxazole-trimethoprim tablets or one double-strength tablet (800 mg sulphamethoxazole + 160 mg trimethoprim)

*Co-trimoxazole oral suspension is 40 mg trimethoprim + 200 mg sulphamethoxazole per 5 mL.

regimens have comparable efficacy but the 480 mg once daily regimen has a lower rate of side effects [62]. A Markov decision model analysis, using data derived from a meta-analysis, showed that these regimens are superior to other regimens in terms of efficacy, but that as life expectancy with HIV-1 infection increases, the 480 mg once daily regimen may have advantages because of the lower rate of associated drug toxicity [64]. The regimen of TMP-SMX 960 mg three times a week has comparable efficacy to nebulized pentamidine or dapsone plus pyrimethamine prophylaxis [65] but may be less effective than 960 mg once daily as one randomised study showed a greater rate of PCP in individuals taking TMP-SMX 960 mg three times a week, compared to the once-daily dosing in on-treatment analysis [66]. Cross-protection is also provided by TMP-SMX against toxoplasmosis and certain bacterial infections [63]. Other prophylactic regimens have been shown to have similar efficacy as either primary or secondary prophylactic agents [62,63,66–68]. However, some, such as dapsone, lack the benefits of broad cross-prophylaxis seen with TMP-SMX, whilst others, such as nebulized pentamidine, are less effective at low CD4 cell counts and following PCP, when used as secondary prophylaxis [69]. Patients who have not tolerated treatment doses of TMP-SMX are often able to take the drug at the lower doses used for secondary prophylaxis [63].

The optimal management of patients who develop intolerance to co-trimoxazole is not determined. Desensitization is a frequently used strategy though equally effective strategies include treating through the rash or stopping and restarting at full dose. Desensitization can be attempted 2 weeks after a non-severe (grade 3 or less) co-trimoxazole reaction that has resulted in a temporary interruption of co-trimoxazole. It has been shown to be successful in most individuals with previous hypersensitivity and rarely causes serious reactions [70,71]. Desensitization should not be attempted in individuals with a history of grade 4 reactions to previous co-trimoxazole or other sulpha drugs. Various desensitization protocols exist. Table 3.4 is reproduced from the World Health Organization guidelines on the use of co-trimoxazole prophylaxis for HIV infection [72].

3.4.6 Impact of HAART

- Early initiation of HAART is favoured in individuals with PCP (category IIb recommendation).
- Individuals with CD4 T-cell counts >200 cells/μL for more than 3 months can discontinue PCP prophylaxis (category Ib recommendation).

The optimal time of initiation of HAART after PCP remains to be determined. One randomized trial of patients with opportunistic infections (approximately two-thirds of whom had PCP) demonstrated that HAART was associated with a significant reduction in mortality, but no evidence of increased IRIS when initiated early (within 2 weeks) compared to deferred therapy, i.e. at approximately 6 weeks after initiation of treatment for the opportunistic infection [73]. Whilst this study supports early treatment, it does not show whether immediate treatment at time of PCP diagnosis or waiting for a response to PCP treatment (usually within 4–7 days) is the best strategy. Furthermore, recruitment to the study excluded those with severe laboratory abnormalities and required patients to be able to take oral medication – suggesting possible pre-screening selection bias in favour of less sick patients. Case reports of acute inflammatory syndromes, predominantly in the first 2 weeks of HAART, exist [74] but although IRIS has been reported following early use of HAART post-PCP [75], this appears to be relatively infrequent. Based on this information, some clinicians would treat immediately whilst others may prefer to see a clinical response to PCP treatment.

The improvements in systemic and local immunity following continuous use of HAART translate into a very low risk of PCP if prophylaxis is discontinued in populations with CD4 T-cell counts sustained >200 cells/μL for more than 3 months [76,77]. In practice this is usually undertaken when an individual's plasma HIV viral load is persistently at undetectable levels. If the peripheral CD4 count falls below 200 cells/μL, PCP prophylaxis should be recommenced. A recent observational study involving over 23 000 individuals has suggested that episodes of PCP are no more frequent in individuals with CD4 T-cell counts of 100–200 cells/μL and an undetectable HIV viral load (defined in the COHERE study as <400 copies/mL) who

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do not receive prophylaxis than in those who do [78]. A second smaller observational study also suggested that PCP prophylaxis could be stopped in individuals with a CD4 T-cell count <200 cells/μL when the viral load is undetectable. This study did not define the CD4 T-cell count threshold at which this could be performed [79]. On the basis of these findings some providers may consider stopping PCP prophylaxis in individuals with CD4 counts 100–200 cells/μL, persistently undetectable HIV viral loads (<50 copies/mL) and maximal adherence to their HAART regimen. Healthcare providers should be aware that this is an evolving area and there are no randomised clinical studies to inform clinical practice and a formal recommendation to stop therapy in most cases in this range cannot currently be made. This option should therefore only be considered in selected individuals where there is felt to be some clear advantage to stopping prophylaxis at a CD4 T-cell count 100–200 cells/μL, generally for reasons of treatment toxicity or to improve adherence to other medications. Discussions with patients regarding discontinuing HAART in such circumstances must emphasise that the evidence to support this option is still limited and falls outside general guidance to stop prophylaxis only at CD4 T-cell counts >200 cells/μL. Regardless of these considerations, individuals with a CD4 T-cell count <100 cells/μL should continue PCP prophylaxis.

Subjects with a proven episode of PCP at CD4 T-cell counts >200 cells/μL may require lifelong prophylaxis.

3.5 Bacterial pneumonia

3.5.1 Background and epidemiology

HIV-related bacterial infection of the lower respiratory tract is common and occurs at all levels of immunosuppression. Risk factors for HIV-related bacterial pneumonia are declining CD4 lymphocyte count, cigarette smoking and injecting drug use [80]. The SMART study identified that a structured treatment interruption was associated with an increased incidence of bacterial pneumonia implying that a detectable viral load may be an additional risk factor for bacterial pneumonia [81]. It also identified cigarette smoking as a risk factor even when the HIV viral load was undetectable.

Recurrent pneumonia (two or more episodes in a 12-month period) is classified as AIDS-defining [82]. The aetiology of community-acquired pneumonia (CAP) among HIV-seropositive individuals is similar to that of the general population with *Streptococcus pneumoniae* and *Haemophilus influenzae* predominating [83,84]. *Staphylococcus aureus* has been reported at a greater frequency than in the general population [84]. *Pseudomonas aeruginosa* has been noted more commonly at low CD4 T-cell counts. Although atypical pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydophila* (*Chlamydia*) *pneumoniae* have not been frequently reported in HIV-related bacterial pneumonia, this may reflect diagnostic difficulties, and there are data to support that these occur at the same frequency in HIV-seropositive and HIV-seronegative populations [85–87]. As with immunocompetent individuals, Gram-negative pathogens should be considered especially likely in those who develop pneumonia when hospitalized. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an increasingly recognized pathogen [88,89]. Rare organisms such as *Rhodococcus equi* and *Nocardia* spp have been reported in association with HIV [90,91].

3.5.2 Presentation

Presenting symptoms are similar to HIV-seronegative individuals and typically have an acute onset (hours to days) [83,92,93]. The classical physical signs are those of lung consolidation. The peripheral white blood count (WBC) is usually elevated but may be low in more severe cases. When pneumonia is suspected a chest radiograph should be obtained. Radiological features are similar to HIV-seronegative individuals. Much higher rates of bacteraemia have been reported in HIV-seropositive compared to HIV-seronegative populations [83].

- Where a purulent sputum sample can be obtained prior to the first dose of antibiotics, this should be sent for Gram stain and culture to guide therapy. In cases requiring hospitalization, a blood culture should also be obtained (category IV recommendation).

In uncomplicated cases further lung sampling either by sputum induction or bronchoscopy with BAL should not be required; but bronchoscopy must be considered in cases that fail to respond to initial therapy and induced sputum or bronchoscopy in all cases with risk factors for PCP or TB.

3.5.3 Treatment

Initial anti-microbial treatment is usually empirical and should be chosen according to: (a) pneumonia severity; (b) the likelihood of particular pathogens as indicated by risk factors; (c) the potential for antibiotic resistance; and (d) potential toxicities. A number of guidelines developed to guide the management of CAP in HIV-seronegative individuals exist and the possible regimens suggested in these guidelines are adapted from them (see Table 3.5) [94–97].

- HIV-seropositive individuals with community-acquired pneumonia should be treated as per HIV-seronegative populations (category IV recommendation).

Antibiotic prophylaxis is not indicated for bacterial pneumonia. The capsular polysaccharide vaccine protects against 23

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Table 3.5 Possible initial empirical antibiotic regimens for suspected community-acquired pneumonia

Severity	Possible regimen	Alternative regimen
Non-severe	po amoxicillin	po macrolide or doxycycline
Moderately severe	po amoxicillin *and* macrolide or doxycycline **or** iv co-amoxiclav or second or third-generation cephalosporin *and* macrolide or doxycycline	po fluoroquinolone with anti-pneumococcal activity (e.g. levofloxacin or moxifloxacin) or iv fluoroquinolone with anti-pneumococcal activity
Severe	iv co-amoxiclav or third-generation cephalosporin *and* iv macrolide	iv fluoroquinolone with anti-pneumococcal activity

pneumococcal serotypes. The Department of Health includes HIV-seropositive individuals amongst the 'high-risk' groups for whom vaccination is recommended [98]. Pneumococcal and Haemophilus vaccination strategies are discussed in the British HIV Association Immunization guidelines [99].

3.5.4 Impact of HAART

The effects of HAART have been demonstrated *in vivo* through a reduced risk of bacterial pneumonia in individuals using antiretrovirals [84,100]. However, its decline has been less marked than for opportunistic infections [1].

3.6 *Cryptococcus neoformans*

3.6.1 Background and epidemiology (see section 2.4 Cryptococcus neoformans)

3.6.2 Presentation

The presenting symptoms may be indistinguishable from PCP, with fever, cough (which may be productive), exertional dyspnoea and pleuritic chest pain often present [101,102]. Chest radiographs show solitary nodules, consolidation, interstitial infiltrates, cavities, intrathoracic lymphadenopathy or pleural effusions [102,103]. Diffuse interstitial infiltrates, which may contain small nodules or have a miliary appearance [104], are most common in those with advanced immunosuppression or those with co-infections [102,103]. As with PCP, pneumothoraces may develop [105]. Disseminated disease is however the most common presentation (see section 2.4 *Cryptococcus neoformans*).

3.6.3 Diagnosis

C. neoformans is identified in induced sputum, BAL or pleural fluid by Giemsa stain, Indian ink staining (which reveals an encapsulated yeast) or by calcofluor white with fluorescence microscopy. Cryptococcal antigen can be detected in BAL; sensitivity 100% and specificity 98% [106]. The yeast can be cultured from BAL or biopsy specimens using blood agar or fungal media such as Sabouraud media [102]. Diagnosis usually requires culture of the yeast with or without a positive antigen test or staining of yeast on BAL or pleural fluid. Biopsy specimens can be stained with special fungal stains such as Grocott–Gomori methenamine silver. Blood culture or serum cryptococcal antigen assay is frequently positive and suggest disseminated disease but may be negative.

3.6.4 Treatment

- Pulmonary cryptococcosis is usually treated as per CNS infection (category III recommendation).
- Pulmonary cryptococcosis, when focal and not associated with hypoxia or positive CSF exam, may be treated initially with fluconazole 400 mg od (category III recommendation).

In cases with pulmonary cryptococcosis a CSF examination should be performed to determine whether meningitis is present (category III recommendation). In general, treatment is per meningitis with a regimen including liposomal amphotericin B (see section 2.4 *Cryptococcus neoformans*) [102]. If the CSF exam is negative, and (1) there is no other evidence of dissemination, (2) radiological infiltrates are focal and (3) there is no hypoxia, treatment with fluconazole, 400 mg od for the initial 10 weeks and 200 mg od po after this, is an alternative strategy (category III recommendation) [102].

3.6.5 Prophylaxis and *3.6.6 Impact of HAART (see section 2.4 Cryptococcus neoformans)*

3.7 Aspergillosis

3.7.1 Background and epidemiology

Aspergillus spp colonize the lung, in particular of individuals with underlying lung disease. Invasive aspergillosis (IA) occurs when the fungus invades the parenchyma and dissemination to other organs may occur in HIV-seropositive individuals [107]. IA is, however, rare in individuals living with HIV-1 infection in the absence of other risk factors such as neutropenia, transplantation or glucocorticoid use.

3.7.2 Presentation

Fever, cough and dyspnoea are frequent presenting features of IA and are often insidious in onset [108]. Pleuritic chest pain may occur. Haemoptysis is rare. A rare alternative syndrome described in individuals living with HIV-1 infection is tracheobronchitis due to aspergillosis [109]. These individuals have ulcerative or nodular lesions in the airway and usually have additional risk factors for

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aspergillosis such as neutropenia or glucocorticoid use. Clinical symptoms include fever, cough, dyspnoea, wheezing and stridor, while some cases may progress to IA.

3.7.3 Diagnosis

Diagnosis of the various forms of aspergillosis requires a combination of radiological and microbiological tests. CT scans of the chest provide better delineation of lesions and identify additional cavities or nodules [110]. Invasive pulmonary aspergillosis (IPA) is identified when either a compatible clinical syndrome is associated with a biopsy specimen that demonstrates *Aspergillus* spp. by culture or histopathology or alternatively is associated with both a consistent clinical plus radiological appearance and with a positive microbiological sample from sputum or BAL. Tracheobronchitis due to aspergillosis can be visualized by bronchoscopy.

- Special fungal stains such as KOH stains of sputum or BAL and Grocott–Gomori methenamine silver stains or equivalents on biopsy specimens should be obtained on all respiratory specimens from HIV-seropositive individuals with pulmonary syndromes of undetermined aetiology (category IV recommendation).
- Fungal cultures should be requested on all samples as the definitive method of proving speciation (category IV recommendation).

The galactomannan test is an enzyme-linked immunosorbent assay that detects the presence of a cell wall constituent of *Aspergillus* spp. [111]. It is commonly used in haematology patients but few data are available in the setting of HIV infection. False positives may occur, in a variety of settings, including in individuals receiving piperacillin-tazobactam [112].

3.7.4 Treatment

Due to the declining incidence of IA, the newer antifungal agents such as voriconazole and caspofungin have not been compared head-to-head or specifically studied in an HIV-seropositive population with invasive aspergillosis.

- On the basis of trials involving largely HIV-seronegative individuals, but including small numbers of HIV-seropositive individuals, primary therapy for invasive pulmonary aspergillosis is with voriconazole (category IV recommendation) [113].

Voriconazole is administered at 6 mg/kg bd, as a loading dose for 24 h, and then 4 mg/kg bd for at least 7 days, followed by 200 mg bd po to complete 12 weeks' therapy. This regimen is superior to amphotericin B deoxycholate in treatment of IA, as evidenced by improved response rates and decreased side effects, though the basis for this observation is a study that did not compare voriconazole directly with liposomal amphotericin B and the primary statistical end-point was evidence of non-inferiority [113]. Liposomal amphotericin B 3 mg/kg od iv is the main alternative to voriconazole. Caspofungin 70 mg loading dose and 50 mg od iv thereafter is an alternative if neither voriconazole nor liposomal amphotericin B can be used and is the preferred agent if significant renal or hepatic disease is present [114]. Posaconazole 200 mg qid or 400 mg bd po is another alternative to voriconazole or liposomal amphotericin B. In practice, individuals will usually receive dosing qid while in hospital, often with food supplements to enhance absorption. They then can switch to the bd schedule when discharged home and better able to tolerate a full meal, which is needed to optimise absorption at the bd dose. Posaconazole oral solution po is, therefore an alternative for individuals intolerant or resistant to standard therapy for IA [115].

Initial therapy should be continued until clinical and radiological evidence of a response is detected, typically for at least 4–6 weeks. Therapy should then be continued with an oral azole such as voriconazole for a minimum of 12 weeks. A prolonged period of maintenance therapy with an agent such as itraconazole oral solution 200 mg bd po or voriconazole 200 mg bd po should be considered for chronic aspergillosis syndromes (conditions in which there is no evidence of parenchymal invasion) [116]. Azoles have multiple drug interactions and therapeutic drug monitoring should be performed to optimise dosing of voriconazole, posaconazole or itraconazole [117] (see Table 3.6).

3.7.5 Prophylaxis

- Routine prophylaxis for pulmonary aspergillosis is not warranted (category IV recommendation).

3.7.6 Impact of HAART

There is little information concerning trends in invasive pulmonary aspergillosis but the incidence appears to have declined post-HAART [118]. Case reports exist of individuals who have developed chronic necrotizing pulmonary aspergillosis as an IRIS following HAART [119].

3.8 Cytomegalovirus (CMV)

3.8.1 Background and epidemiology

CMV is a DNA virus and member of the human β-herpesvirinae. CMV establishes latency and individuals with decreased cell-mediated immunity can develop severe disease due to reactivation or occasionally primary infection/superinfection. Reactivation of latent virus is common in those with advanced immunosuppression and frequently does not cause end-organ disease. Detection of CMV in urine, blood or BAL without evidence of end-organ involvement implies CMV infection but not disease. CMV isolation in BAL

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Table 3.6 Potential pulmonary and antiretroviral drug interactions

Drug name	Interaction with antiretroviral	Action required
Antibiotics		
Atovaquone	Zidovudine levels can be increased	Monitor for signs of zidovudine toxicity
	Ritonavir as an antiretroviral or pharmacokinetic booster can decrease the levels of atovaquone	Manufacturer's information recommends careful monitoring for therapeutic effect when used with ritonavir.
Clarithromycin	NNRTIs, PIs and boosted PIs can alter clarithromycin levels	See individual antiretroviral manufacturer's information
	Maraviroc likely to be increased	Reduce dose of maraviroc (150 mg od)
Rifabutin	Boosted PIs increase rifabutin levels	Reduce rifabutin dose (150 mg three times weekly)
	NNRTIs can reduce rifabutin levels	Consider increasing rifabutin dose (450 mg od)
	Etravirine and rifabutin levels reduced when used together	Use with caution
Rifampicin	NNRTI levels reduced	Increase dose of efavirenz (800 mg od) depending on patient's weight Contraindicated with etravirine and nevirapine (some units increase nevirapine dose)
	PI levels significantly reduced	Contraindicated with PIs (including boosted PIs)
	Maraviroc levels reduced	Increase maraviroc dose (600 mg bd)
	Raltegravir levels reduced	Consider increasing dose of raltegravir (800 mg bd)
Antifungals		
Amphotericin	Tenofovir	Caution – increased risk of renal toxicity with concurrent or recent use.
Itraconazole	Ritonavir increases itraconazole levels	Avoid high doses of itraconazole Caution with boosted PIs – some PI levels increased
	Efavirenz, etravirine and nevirapine reduce itraconazole levels	Consider alternative, or increasing dose Monitor clinical effect
	Maraviroc levels increased	Reduce maraviroc dose (150 mg bd)
Voriconazole	Efavirenz levels increased and voriconazole levels reduced	Avoid combination
	Etravirine and voriconazole levels are both increased	No dose adjustment required – monitor
	Lopinavir/ritonavir reduces voriconazole levels.	Do not use together
Fluconazole	Zidovudine levels increased	Caution – monitor for adverse effects
	Nevirapine levels increased	Caution – monitor for adverse effects
Posaconazole	Efavirenz reduces posaconazole levels	Avoid combination unless benefit to patient outweighs risk
	Atazanavir levels increased	Caution – additional monitoring for toxicity (bilirubin levels)
	Other PIs – levels possibly increased	Monitor for signs of toxicity
Caspofungin	Efavirenz and nevirapine reduce levels	Increase caspofungin dose to 70 mg od for those <80 kg

Antiretroviral drugs, especially the NNRTIs and boosted PIs, have several important drug–drug interactions. This table lists some examples of drug–drug interactions with antiretrovirals and drugs used in pulmonary infection. As data and advice changes frequently, this information should always be interpreted in conjunction with the manufacturer's information (www.medicines.org.uk). Other useful web-based reference sources include the Liverpool HIV drug information website (www.hiv-druginteractions.org) and the Toronto Clinic (www.hivclinic.ca/main/drugs_interact.html).

(by culture or PCR) is common in individuals with HIV infection, who have low CD4 T-cell counts [120,121].

3.8.2 Presentation

Typical symptoms are dry non-productive cough and exertional dyspnoea with fever; and this presentation is similar to many other pulmonary conditions [120,122]. Hypoxaemia is often marked [120]. The chest radiograph and CT scan most often show bilateral interstitial infiltrates or ground glass attenuation, but unilateral alveolar consolidation, bilateral nodular opacities, pleural effusions or rarely cavities or hilar adenopathy may occur [120,122,123]. There may be concomitant evidence of extra-pulmonary CMV [120] and a dilated eye examination should be performed to rule out CMV retinitis.

3.8.3 Diagnosis

The major diagnostic challenge is to differentiate CMV shedding in respiratory secretions from cases with CMV pneumonitis. Culture, positive PCR or antigen assay for CMV from BAL or biopsy specimen do not distinguish CMV shedding from pneumonitis, and hence must be interpreted with caution [124,125]. A negative culture result, with its high negative predictive value, however, does reasonably exclude CMV pneumonia [126].

- Diagnosis of CMV pneumonia requires a biopsy specimen to provide evidence of pulmonary involvement in association with a compatible clinical syndrome (category III recommendation).

Evidence of intranuclear or intracytoplasmic viral inclusions, positive immunostaining for CMV antigens or detection of CMV by molecular techniques such as *in situ* hybridization on a pulmonary biopsy specimen establishes the diagnosis in the setting of a compatible clinical syndrome [120].

3.8.4 Treatment

CMV replication in the respiratory tract is most frequently only a marker of immunosuppression and not of pneumonia.

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- The majority of individuals in whom microbiological tests on BAL, or biopsy, demonstrate CMV should not receive treatment for CMV (category III recommendation).
- Cases with a compatible clinical syndrome, positive microbiology for CMV in BAL or biopsy and positive histology on biopsy or BAL without an alternative microbiological cause of respiratory disease should receive anti-CMV treatment (category III recommendation).

This approach is supported by evidence that when treatment is withheld, in individuals with evidence of CMV on BAL or biopsy, clinical outcome is not adversely altered [127]. However, the benefits of treatment to the select subset of individuals who have evidence of a compatible clinical syndrome, positive microbiology and histology for CMV and no alternative diagnosis have been suggested by retrospective case series that show improved clinical outcomes with treatment [121]. The management of individuals with positive histology for CMV but identification of a second pulmonary pathogen is also controversial.

- In co-infected individuals it is reasonable to start by treating the co-pathogen first and to only treating the CMV if there is a failure of clinical response (category IV recommendation).
- Standard therapy for CMV pneumonitis is with ganciclovir (category III recommendation).

Ganciclovir is administered at 5 mg/kg bd iv for 21 days [120]. Foscarnet (90 mg/kg bd iv) or cidofovir (5 mg/kg per week iv) are alternatives in those who are not responsive or who are intolerant to ganciclovir therapy although data in CMV pneumonia in HIV-seropositive individuals are limited [128]. Valganciclovir 900 mg bd po is an alternative for individuals able to tolerate oral therapy or for whom a switch from intravenous therapy is indicated.

3.8.5 Prophylaxis

Although there is no clinical trial evidence to support the use of CMV prophylaxis, in the exceptional patient with a persistently low CD4 count, detectable CMV viraemia and no HIV treatment options, CMV prophylaxis may be considered. The vast majority of patients with low CD4 T-cell counts will not require CMV prophylaxis. Valganciclovir prophylaxis (900 mg od or bd) can be considered in selected individuals when the CD4 count remains <50 cells/μL, there is persistent detection of CMV DNA or CMV viraemia, coupled with a low risk of prompt immune reconstitution by HAART and there is no evidence of CMV end-organ disease (category IV recommendation), since detection of CMV DNA is a risk factor for death in this setting over and above the risk of low CD4 T-cell count or HIV viraemia [129]. Maintenance therapy with valganciclovir is not initially required after treatment of CMV pneumonia but may be added if CMV pneumonia relapses or if extra-pulmonary disease is present.

- Valganciclovir may be considered as primary prophylaxis in selected patients with persistent immunosuppression and detectable CMV DNA; or as secondary prophylaxis in those with relapse of CMV pneumonia after appropriate primary therapy (category IV recommendation).

3.8.6 Impact of HAART

HAART has decreased the incidence of all forms of CMV disease and CMV pneumonia is now rare. CMV IRIS occurs more commonly as an ocular complication, although case reports of CMV IRIS in the lung exist [130].

3.9 Influenza A virus (IAV)

3.9.1 Background and clinical presentation

Studies of HIV-seropositive individuals have not consistently demonstrated a greater incidence of IAV; they have, however, suggested a greater risk of more severe disease [131,132], but this likely reflects an association with concomitant medical comorbidities [133].

3.9.2 Diagnosis

In suspected cases diagnosis is confirmed by detection of viral antigen or viral culture from nasopharyngeal aspirate (NPA) or nasal swab specimen [131].

3.9.3 Treatment

- HIV-seropositive individuals should receive the neuraminidase inhibitor oseltamivir (assuming the majority of circulating strains in a given flu season show susceptibility) (category IV recommendation).

HIV-seropositive individuals should be treated when IAV is documented, and fever >38.0 °C has been present for less than 48 h, although for individuals with significant immunosuppression (CD4 T-cell count <200 cells/μL) treatment may be administered if afebrile or if symptoms have been present for more than 48 h. These recommendations are made in view of the increased incidence of IAV complications in HIV-seropositive individuals [131,132], but there are no trials of treatment in HIV-seropositive groups per se, only case series from treatment of patients at high-risk of complications of IAV in general. Similarly in cases associated with H1N1v ('Swine flu') treatment has often been prescribed regardless of symptom duration. Oseltamivir 75 mg bd po for 5 days is currently the preferred neuraminidase inhibitor [134,135]. Inhaled zanamivir 10 mg (two puffs) bid by inhalation device for 5 days is an alternative [136] and has even been suggested as the preferred agent for HIV-seropositive adults with significant immunosuppression in some guidelines on the

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basis of increased rates of oseltamivir resistance in this group [137]. Most pandemic IAV strains in 2009–2010 retained susceptibility to neuraminidase inhibitors, but strains with reduced susceptibility to oseltamivir have been reported occasionally in individuals living with HIV [138]. In addition, seasonal IAV strains in 2008–2009 were frequently oseltamivir-resistant [139] and the selection of the most appropriate neuraminidase inhibitor must be made in light of the prevailing susceptibility of the strain(s) circulating in a given 'flu season' in consultation with local virologists. While many of these strains remain susceptible to zanamivir at present, multi-resistant strains have been reported in other immunocompromised groups [140]. Some authorities have suggested combination therapy will be required, particularly for immunocompromised patients, in the future and clinical trials are exploring this possibility in patients (not specifically HIV-seropositive individuals) with severe infection [141,142].

For critically ill individuals parenteral formulations of neuraminidase inhibitors, currently available for compassionate use or through expanded access programmes, include iv peramivir and zanamivir but there are currently no data on their use in HIV-seropositive individuals. Neuraminidase inhibitors have proven efficacy against IAV in individuals considered at high risk of IAV complications [143]. It is recommended that immunocompromised patients also receive doxycycline 200 mg stat then 100 mg od or co-amoxiclav 625 mg tid po with clarithromycin 500 mg bd po as an alternative, all for 7 days during an episode of IAV but again no specific data are available for HIV-seropositive populations [144]. If pneumonia develops, coverage should be as per the guidelines above for community-acquired pneumonia but if patients fail to respond promptly, there are epidemiological concerns that methicillin-sensitive or -resistant *Staphylococcus aureus* (MSSA/MRSA) may be causing bacterial super-infection or there is a significant incidence of bacterial super-infection with MSSA/MRSA, then antibacterial therapy should also target these organisms.

3.9.4 Prevention

IAV vaccination should be offered to all HIV-seropositive individuals every 'flu season (category Ib recommendation) [97,99,145]. However, in certain seasons incomplete coverage by the vaccine strains may result in increased levels of IAV amongst HIV-seropositive individuals [146].

- HIV-seropositive individuals should receive IAV vaccination each year (category Ib recommendation)

HIV-seronegative, immunocompromised individuals have prolonged shedding of IAV but there are limited data on the duration of shedding in HIV-seropositive individuals [147]. However, this possibility should be considered and appropriate droplet infection control policies implemented for both outpatients and in-patients with advanced immunosuppression. Recent data for pandemic H1N1 IAV have shown no evidence for prolonged viral shedding in a group of HIV-seropositive children, with CD4 T-cell counts >350 cells/μL receiving HAART but not neuraminidase inhibitors, when compared to historical controls [148]. Moreover when oseltamivir was prescribed it significantly shortened the duration of shedding, therefore IAV treatment may reduce secondary transmission in HIV-seropositive individuals, regardless of symptoms and treatment of index cases may be considered as a preventative measure (category IV recommendation).

In line with recommendations for the general population the use of antiviral prophylaxis is not routinely required in HIV-seropositive individuals exposed to IAV [137]. For individuals who are (1) significantly immunosuppressed (CD4 T-cell count <200 cells/μL), (2) have not received vaccination or are believed to be at significant risk of vaccine non-response due to either immunosuppression or recent administration and (3) have been exposed within the last 48 h, antiviral prophylaxis may be considered although there are no HIV-specific data currently on which to base this recommendation (category IV recommendation). Oseltamivir is most often prescribed for prophylactic use in the general population using 75 mg od for 10 days although in more significantly immunosuppressed individuals or in the presence of oseltamivir-resistance, inhaled zanamivir 10 mg od for 10 days may be considered [137]. Some authorities recommend doubling the dose of these agents to levels equivalent to treatment doses (oseltamivir 75 mg bd orally or zanamivir 10 mg bd by inhalation) for 10 days in more severely immunocompromised individuals. This area, like treatment recommendations discussed above, changes from year to year therefore practitioners are referred to national guidance on IAV management, which varies from year to year. In the UK these guidelines are provided by the Health Protection Agency [137].

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4 Gastrointestinal opportunistic infections

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4.1 Methods

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

4.2 General overview

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

4.3 Oesophagitis

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

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

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

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

Table 4.1 Major causes of HIV-related diarrhoea

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

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

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

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

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

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

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

4.4 Diarrhoea

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

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

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

4.4.1 Acute diarrhoea due to bacteria and viruses

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.4.2 Cytomegalovirus

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

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

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

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

Table 4.2 Gastrointestinal presentations of CMV disease

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

OGD, oesophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography.

4.4.2.4 Treatment

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

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

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

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

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

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

4.4.3 Cryptosporidium spp

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

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

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

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

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

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

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

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

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

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

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

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

4.4.4 Microsporidiosis

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

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

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

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

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

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

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

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

4.4.4.6 Prevention. As for Cryptosporidium.

4.4.5 Other parasites and helminths causing diarrhoea (usually chronic)

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

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

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

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Table 4.3 Treatment for selected parasites in association with HIV

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

ZN, Ziehl–Neelsen.

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

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

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

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

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

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

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5 Ocular infections

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5.1 CMV retinitis (CMVR)

5.1.1 Background and epidemiology

For potential CMV and antiretroviral drug–drug interactions please refer to Table 5.1.

Since the advent of potent antiretroviral therapy in 1996 the incidence, clinical features and long-term prognosis of CMV retinitis have changed dramatically. Highly active antiretroviral treatment (HAART) has significantly decreased the number of patients with CD4 counts of <50 cells/μL and therefore the proportion of patients at risk of developing CMVR, as well as significantly prolonging disease-free intervals in patients with pre-existing CMVR [1–3].

In spite of improvements in the era of potent antiretroviral treatments, CMVR remains a significant clinical problem as well as the leading cause of ocular morbidity for patients with AIDS [4]. Despite improvements in immune function (immune reconstitution) due to HAART, new cases of CMVR continue to occur because of late diagnosis of HIV, poor adherence or poor tolerance of treatment and failure of antiretroviral treatment.

5.1.2 Presentation

CMVR usually presents in persons who are severely immunosuppressed with CD4 counts of <50 cells/μL. It may affect one eye at first, but without systemic treatment or improvement of the immune system the other eye usually becomes affected [5]. Symptoms depend on the site and severity of retinal involvement of CMV. Common clinical presentations include floaters, blind spots, blurred vision or a sudden decrease in vision. However, approximately 15% of patients with active CMVR are asymptomatic.

- Routine screening with dilated indirect ophthalmoscopy is recommended at 3-monthly intervals in patients with CD4 counts less than 50 cells/μL [6].

5.1.3 Diagnosis

CMVR is a clinical diagnosis. Virological confirmation is not ordinarily required. Visualization of the retina should be performed through a dilated pupil to enable peripheral lesions to be seen. Once the diagnosis of CMVR is suspected urgent assessment is required by an ophthalmologist to confirm the diagnosis and advise on appropriate treatment.

5.1.4 Treatment

Treatment is indicated for *incident* cases of CMVR and *progression* (extension of CMVR by 750 μm along a 750 μm-wide front) or *reactivation* (development of a new CMVR lesion either at the edge of an old lesion or at a new focus) of pre-existing CMVR [7].

Treatment limits progression of retinitis and reduces the risk of blinding complications such as retinal detachment

Table 5.1 Potential CMV and antiretroviral drug interactions

Drug name	Interaction with antiretroviral	Action required
Antiviral		
Valganciclovir/ganciclovir	Zidovudine levels increased and valganciclovir/ganciclovir levels reduced (slightly)	Monitor for signs of haematological toxicity
	Didanosine levels increased with both oral valganciclovir, ganciclovir and IV ganciclovir	Monitor
	Lamivudine	Not recommended to be used together. Seek HIV specialist pharmacist advice
	Tenofovir	Caution – monitor for signs of increased renal toxicity with concurrent or recent use of valganciclovir/ganciclovir
Foscarnet	Lamivudine	Not recommended to be used together. Seek HIV specialist pharmacist advice
	Tenofovir	Caution – monitor for signs of increased renal toxicity with concurrent or recent use of foscarnet
Cidofovir	Zidovudine levels increased	Monitor for signs of zidovudine toxicity Consider potential interaction with probenecid which is coadministered with cidofovir
	Tenofovir	Caution – monitor for signs of increased renal toxicity with concurrent or recent use of cidofovir

This table lists some examples of drug–drug interactions with antiretrovirals and drugs used for the treatment of cytomegalovirus. As data and advice change frequently, this information should always be interpreted in conjunction with the manufacturer's information (www.medicines.org.uk). Other useful web-based reference sources include the Liverpool HIV drug information website (www.hiv-druginteractions.org) and the Toronto Clinic (www.hivclinic.ca/main/drugs_interact.html).

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and macular involvement of CMVR [8]. Systemic anti-CMV treatment also provides prophylaxis to an unaffected contralateral eye. Intravitreal injections or implants containing anti-CMV treatment provide more expedient loading dosages if required and are localized treatments for those patients unable to tolerate systemic therapy.

Treatment of CMVR consists of an induction period of between 2 and 4 weeks of therapy followed by a maintenance period in which the drug dosage is lower. The duration of maintenance therapy depends on immune recovery with HAART and lack of evidence of CMVR progression or reactivation.

In a randomized study published by the Valganciclovir Study Group, the median time to progression of CMVR was 125 days for patients originally assigned to intravenous ganciclovir and 160 days for patients originally assigned to oral valganciclovir. The proportions of patients in each group having a satisfactory response to induction therapy were similar between the two drugs, as were the rates of adverse events [7].

- Systemic anti-CMV therapy should be considered as the first-line treatment strategy for CMVR (category 1 recommendation).
- Oral valganciclovir is the preferred induction and maintenance therapy but iv ganciclovir, iv foscarnet, and iv cidofovir can be considered if there are potential issues with adherence, absorption or specific contraindications to oral therapy (category Ib recommendation).

The standard treatment regimens used in induction include oral valganciclovir 900 mg bd, iv ganciclovir 5 mg/kg bd, iv foscarnet 90 mg/kg bd. Intravenous cidofovir (5 mg/kg) is given weekly for 2 weeks.

All intravenous dosages need adjustment in cases of renal impairment. Close monitoring for adverse events is required as anti-CMV medications may cause significant toxicities such as renal and electrolyte abnormalities, and bone marrow suppression.

The additional use of a ganciclovir implant or intravitreal injections of ganciclovir/foscarnet is recommended for CMVR affecting zone 1 (see Fig. 5.1) [9].

Induction and maintenance with a ganciclovir implant should be considered in patients for whom systemic therapy is contraindicated. The median time to progression of CMVR with a ganciclovir implant was approximately 220 days in the pre-HAART era [9].

5.1.5 Maintenance and duration of anti-CMV treatment for CMVR

The standard treatment regimens used in maintenance include oral valganciclovir 900 mg od, iv ganciclovir 5 mg/kg daily or 6 mg/kg/day for 5 days of the week, iv foscarnet 90 mg/kg od daily or 120 mg/kg for 5 days of the week. Intravenous cidofovir (5 mg/kg) is given fortnightly.

Fig. 5.1 Diagram of an entire retina and the zones of CMVR involvement: based on the standardized system published by the UCLA CMV Retinopathy Study Group [51] and the Studies of the Ocular Complications of AIDS (SOCA) [52].

Description of areas of involvement of CMV retinitis: Zone 1, within 3000 μm of the centre of the fovea or 1500 μm from the disc; zone 2, from zone 1 to the ampulla of the vortex veins (equator of the globe); zone 3, from zone 2 to the ora serrata.

CMVR can be expected to relapse in spite of ongoing anti-CMV treatment if immune reconstitution does not occur [7].

Maintenance treatment can be stopped if there is good immune reconstitution (CD4 > 100 cells/μL and undetectable viral loads) [10–13]. This decision should be made following careful discussion between the HIV physician and the ophthalmologist involved in the patient's care.

5.1.6 Reactivation or progression of CMVR

When disease occurs in zones 1 and 2 (see Fig. 5.1), induction is achieved with oral valganciclovir as above. Adjunctive intraocular ganciclovir/foscarnet may also be used. Oral valganciclovir alone is used for induction of treatment with reactivation or progression in zone 3 (see Fig. 5.1) disease.

Failure with systemic ganciclovir in end organ eye disease can be dose or resistance related. Options for treatment are dose increase, if toxicity allows, and implant or intravitreal ganciclovir. Intravitreal foscarnet is an alternative option, as is a switch to foscarnet or cidofovir.

If the individual has failed foscarnet, options are ganciclovir implant or a switch to ganciclovir.

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Importantly, if an implant alone has been utilized, the fact that implants do not release ganciclovir steadily may mean that 'failures' have just ceased to have release of active drug.

Cidofovir failure is rare in end organ eye disease. It cannot be given intravitreally. Failure is rarely due to true viral resistance in the eye.

Combined foscarnet/ganciclovir remains an option in all scenarios.

5.1.7 Resistance to anti-CMV treatment

Ganciclovir-resistant cultures were demonstrated in 25–28% of patients after 9–24 months of treatment in the pre-HAART era. The incidence of viral resistance to ganciclovir has decreased significantly in the HAART era to 9% in a 2-year period [14,15].

5.1.8 Pregnancy and breastfeeding

The management of CMVR in pregnancy is covered in the pregnancy section (see 11 Special considerations in pregnancy). Female patients should be advised to avoid getting pregnant during, and for 1 month after, treatment with cidofovir. Men should not father a child during or within 3 months of cidofovir treatment.

5.1.9 Impact of HAART

As with other opportunistic infections, effective antiretroviral therapy prevents relapses of CMVR and prompt initiation of therapy, where possible, is recommended. CMV-associated IRIS is reported to occur in individuals commencing HAART, and may occur many months after commencement of HAART [16,17]. Specific manifestations include uveitis, retinitis, vitritis, cystic macular oedema and papillitis [18]. The commonest clinical presentation is with a vitritis, which has been reported to occur in 16–63% of individuals commencing HAART with a previous diagnosis of CMVR and is most likely in those with large retinal lesions at baseline [2,19,20]. Immune recovery uveitis (IRU) is an intraocular inflammatory reaction that occurs in patients with CMVR who experience immune reconstitution following antiretroviral treatment [21]. Patients with CMVR involvement of greater than 25% of the retina are at higher risk of IRU [19,22]. It tends to be seen as the CD4 count hovers between 50–150 cells/μL and resolves as it rises further. Long-term ophthalmological follow up is recommended in cases of CMV IRIS involving the eye due to the possibility of retinal neovascularization occurring in some patients years after diagnosis [23]. Treatment of CMV IRIS requires close coordination between an experienced HIV physician and ophthalmologist and often requires corticosteroids either systemically or periocularly [24,25]. Uncontrolled studies suggest a possible additional role of ganciclovir [26].

5.2 Other ocular infections of particular importance in the setting of HIV

5.2.1 Syphilis

Syphilis may manifest in the eye as iritis, vitritis, optic neuritis, papillitis, neuroretinitis, retinal vasculitis or a necrotizing retinitis [4,27].

In the setting of HIV, all cases of ocular syphilis should be investigated for neurosyphilis as CNS involvement occurs at a higher rate in HIV-seropositive patients compared with non-HIV-seropositive patients [28,29]. Syphilis may also have a more aggressive course in HIV-seropositive individuals [27,30,31].

For the specific treatment of syphilis refer to the British Association for Sexual Health and HIV guidelines (2008) [32]. The treatment of ocular syphilis is identical to the treatment for neurosyphilis.

5.2.2 Toxoplasmosis

Pre-HAART data suggests that ocular toxoplasmosis accounts for 0.3–3% of eye infections in HIV-seropositive patients [33–35]. It is much less common than cerebral toxoplasmosis in these patients. Ocular toxoplasmosis is the most common cause of posterior uveitis in immunocompetent individuals [36].

Ocular toxoplasmosis can occur as a reactivation of a pre-natal infestation; however, it has been shown to be frequently acquired postnatally [37]. In HIV-seropositive patients ocular toxoplasmosis occurs at an earlier stage than CMV retinitis. As a result a vitreous inflammatory response can usually be seen on examination. The clinical appearance may be similar to the classic appearance found in immunocompetent patients with a focus of retinochoroiditis adjacent to a chorioretinal scar from previous infestation. There is overlying vitreous haze and cellular response. However, in AIDS atypical presentations have been reported and can include the presence of multiple, large or bilateral lesions. Other atypical manifestations include punctate lesions in deep retina, retinal vasculitis, a pigmentary retinopathy, neuroretinitis and scleritis [38].

The diagnosis is usually made on the basis of clinical suspicion. Corroborating tests include detection of plasma and intraocular fluid anti-toxoplasma antibody titres or detection of toxoplasma DNA in ocular fluids by polymerase chain reaction-based techniques [39]. However, intravitreal assays in this setting are not well validated. Central nervous system involvement should be excluded with magnetic resonance imaging.

Treatment is started in all cases of ocular toxoplasmosis and long-term maintenance therapy is required. Treatment should be systemic in all cases and maintenance therapy may be stopped if there is good immune recovery with

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HAART. The standard multi-drug regimens used in the immunocompetent, such as sulphadiazine and pyrimethamine, have good efficacy; however, problems with toxicity and drug interactions may limit their long-term use. Atovaquone has also been used with success as it has potent activity against the tachyzoite and cyst forms of *Toxoplasma gondii* and has relatively fewer problems with toxicity [40,41].

5.2.3 Varicella zoster virus retinitis

The progressive outer retinal necrosis syndrome (PORN) and acute retinal necrosis syndrome (ARN) are descriptions of an aggressive necrotising retinitis. The most common cause of both is varicella zoster virus (VZV). ARN typically affects healthy individuals and can be caused by herpes simplex virus in younger patients and VZV in older patients [42,43].

The clinical picture is of a rapidly progressive visual loss occurring unilaterally initially. The hallmark is a progressive full-thickness retinal necrosis with confluent lesions spreading inwards from the retinal periphery. There may be associated uveitis but this is less evident in significantly immunocompromised patients, who may experience early macular involvement with no vitritis. Papillitis may occur early and result in visual loss. Retinal haemorrhages may also be present [43–46].

Visual prognosis is poor due to the associated complications of retinal detachment, ischaemic optic neuropathy from vascular occlusion or optic nerve inflammation and macular involvement [43,44,46].

Although vitreous sampling and analysis has a role in the diagnosis of VZV retinitis it is not used routinely for the monitoring of the success of therapy. However, it has been used in the research setting [47,48].

Treatment outcomes are often disappointing, with patients becoming blind within weeks from macular involvement and complications such as retinal detachment. A combination of intravenous ganciclovir alone or in combination with foscarnet, and intravitreal ganciclovir/foscarnet have been used to halt the progression of retinitis; however, intravenous cidofovir is probably the drug of choice, with or without the addition of intravitreal ganciclovir or foscarnet [49,50].

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6 Herpes viruses

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6.1 Introduction

The herpesviruses are a large family of DNA viruses that cause disease in humans. There are three phases of infection: primary infection, latency and reactivation. Immunocompromised individuals are at increased risk of more severe and atypical primary infection and disease associated with reactivation of latent virus.

Herpesviruses are classified into three groups.

1. Alpha herpesviruses (herpes simplex virus 1 and 2, varicella zoster virus). The primary target cell is mucoepithelial with latency developing in nerve cells.
2. Beta herpesviruses (cytomegalovirus, human herpes viruses 6 and 7).
3. Gamma herpesviruses (Epstein–Barr virus and Kaposi's sarcoma herpes virus).

This chapter is concerned with infection associated with alpha herpesviruses. Disease related to CMV reactivation is discussed in organ-specific chapters. Epstein–Barr virus and Kaposi's sarcoma herpes virus are associated with neoplastic disease and are described elsewhere [1].

6.2 Varicella zoster virus

6.2.1 Methods

The PubMed database was searched using the following search headings: HIV, AIDS, herpes zoster, varicella.

6.2.2 Background

Varicella zoster virus (VZV) is a human neurotropic alpha-herpes DNA virus that is usually transmitted by the respiratory route. It is the causative agent of both varicella (chickenpox) and zoster (shingles). Varicella results from primary infection of VZV and is a common childhood illness, usually presenting as a benign self-limiting illness with fever and generalized pruritic vesicular rash.

Following primary infection, VZV establishes lifelong latency in the cells of the dorsal root ganglia. Reactivation results in herpes zoster disease. In HIV-seropositive patients reactivation is more common, and in those with advanced immune deficiency may result in severe and disseminated clinical disease.

6.2.3 Epidemiology

In the general population, the incidence of herpes zoster (shingles) is 1.5–3 per 1000 persons per year. It is seen more frequently in patients aged 60 years and older and in those who are immunocompromised [2–5].

Individuals with HIV infection have significantly higher rates of herpes zoster than the general population [6] with an estimated relative risk of 15 or greater compared to age-matched HIV-seronegative controls [7,8].

Herpes zoster occurs more frequently in HIV-seropositive patients with a CD4 count $<$200–250 cells/μL [9,10] and, unlike the non-immunocompromised individual, recurrences are common and have been reported to occur in up to 20–30% of cases [8,11,12]. The effect of highly active antiretroviral therapy (HAART) is unclear, although one cohort study suggested no change in the incidence from the pre-HAART era [10].

6.2.4 Presentation

6.2.4.1 Varicella. As a consequence of prior infection in childhood, primary varicella infection is uncommon in the HIV-seropositive adult population but if it occurs, can result in severe disease with visceral dissemination, particularly pneumonitis.

6.2.4.2 Zoster. Herpes zoster may occur at any stage of HIV infection, and may be the first clinical evidence of previously undiagnosed HIV infection.

6.2.4.2.1 Cutaneous disease

Herpes zoster usually appears as a localized, erythematous, maculopapular eruption along a single dermatome, but may be multi-dermatomal. Lesions evolve over 1–2 days to form vesicles, pustules and crusts. Vesicles often become confluent, and may form bullae. In HIV-seropositive patients, zoster may be particularly bullous, haemorrhagic, necrotic and painful. Blisters and crusts usually last 2–3 weeks, although necrotic lesions may last for up to 6 weeks and heal with severe scarring. HIV-seropositive persons with herpes zoster are at an increased risk of recurrent episodes [8,10–12], which may be more severe with increasing immune deficiency.

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In patients with advanced HIV disease, prolonged lesion formation, and dissemination of virus can occur. Cutaneous dissemination may be widespread, making it indistinguishable from primary varicella infection. Despite an impaired immune system, the majority of HIV-seropositive patients with zoster do not develop life-threatening complications, and most have an uncomplicated clinical course.

Chronic localized herpes zoster cutaneous lesions have been reported in patients with severe immune deficiency and have been associated with resistance to aciclovir [13,14].

Herpes zoster has also been recognized as a manifestation of immune reconstitution disease [15,16] following initiation of HAART, with a 2–4-fold increase in risk in the first few months of starting HAART. The clinical presentation and natural history does not differ from other HIV-seropositive patients.

6.2.4.2.2 Eye disease

Herpes zoster ophthalmicus (HZO) involves the ophthalmic division of the trigeminal nerve. In addition to skin lesions, involvement of the conjunctiva, cornea and other eye structures can occur resulting in visual loss, keratitis, anterior uveitis, severe post herpetic neuralgia and necrotizing retinopathy.

6.2.4.2.3 CNS disease

In HIV-seropositive patients, herpes zoster dissemination can cause severe disease in the CNS [17]. Multiple clinical presentations have been reported and include multi-focal leukoencephalitis, vasculitis with cerebral infarction, myelitis, ventriculitis, myeloradiculitis, optic neuritis, meningitis and focal brainstem lesions. Herpes zoster CNS disease may occur in the absence of dermatomal lesions and should always be considered in the differential diagnosis of HIV-seropositive patients presenting with neurological disease, especially those with advanced immune deficiency.

6.2.5 Diagnosis

Dermatomal herpes zoster and chickenpox are generally diagnosed empirically on the basis of the clinical appearance of characteristic lesions.

Laboratory studies may be required for confirmation in atypical cutaneous presentation. The diagnostic procedure of choice was formerly the detection of virus antigens expressed on the surface of infected cells obtained directly from cutaneous lesions. Cells were stained with specific fluorescein-conjugated monoclonal antibodies to confirm the presence of VZV antigens. This technique is rapid, and reliable. In the diagnosis of VZV infection, virus culture is less sensitive than direct antigen staining with reported sensitivity of 49% as compared to 97.5% [18]; however, virus culture in a patient with suspected aciclovir-resistant VZV infection would allow for the identification of aciclovir resistance [14]. PCR based diagnosis is more rapid and more sensitive than culture based diagnosis in immunocompetent populations, demonstrating a sensitivity of 100% vs. 29% for culture with a specificity of 100% in one study and has replaced direct antigen staining in many centres [19,20]. There is much less evidence for the performance of these tests in HIV-seropositive groups specifically.

Findings in the CSF of a pleocytosis, mildly raised protein and positive PCR for VZV DNA are supportive of the diagnosis of herpes zoster CNS disease [21,22]. The absence of a positive PCR for VZV DNA in the CSF does not exclude a diagnosis of zoster CNS disease [22]. In series including HIV seropositive and seronegative individuals with compatible clinical disorders the VZV PCR had an 80% sensitivity and 98% specificity for the diagnosis of neurological VZV infection [23]. However interpretation of the PCR result must take into account the full clinical details [22] since at least in immunocompetent individuals transient viral reactivation of unclear significance has been described [24].

Histopathology and PCR for VZV DNA can be helpful in the diagnosis of visceral disease.

6.2.6 Treatment

6.2.6.1 Varicella. Treatment of primary varicella in HIV-seropositive patients should begin as early as possible. There is limited data from studies in HIV-seropositive individuals on which to base recommendations and as pointed out in other published guidelines extrapolation of data from other immunocompromised groups is required [25]. Treatment with intravenous aciclovir (5–10 mg/kg every 8 h) for 7–10 days is advised [26], though more prolonged treatment courses may be required until all lesions have healed. It is possible to switch to oral therapy (800 mg five times per day) when the patient becomes afebrile and there is no evidence of visceral involvement, although this recommendation is based on a study in HIV-seronegative immunocompromised children the majority of whom also received VZV immunoglobulin [27]. In patients with high CD4 cell counts and uncomplicated disease, oral aciclovir may be considered if initiated within 24 h of onset of the varicella rash. Alternative oral agents include famciclovir and valaciclovir though, there is limited data on their use in HIV-seropositive individuals despite extensive anecdotal experience.

6.2.6.2 Zoster. Treatment of zoster in HIV-seropositive patients should begin as soon as possible (preferably within 72 h of onset of the skin rash) and be continued for at least 7 days or until all lesions have dried and crusted.

- For localised dermatomal herpes zoster, oral aciclovir at a dose of 800 mg five times per day is recommended.

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Famciclovir and valaciclovir are alternative agents although data to support their use has thus far only been available in meetings abstracts [28,29], but they may be preferred by some because of the more convenient dosing and their ability to cause higher antiviral levels in the blood as discussed in other guidelines [25]. For severe cutaneous disease or disseminated herpes zoster infection with evidence of visceral involvement, including CNS disease, admission to hospital and treatment with intravenous aciclovir (10 mg/kg every 8 h) is recommended [30,31] and 10–14 days of treatment is usually required, based on the experience in HIV-seronegative immunocompromised individuals (category III recommendation).

- Patients presenting with disseminated herpes zoster infection with visceral involvement should be started on HAART or current ART optimized to improve the level of immune deficiency (category IV recommendation).

6.2.6.3 Aciclovir resistance. Persistent disseminated VZV infection that fails to respond to intravenous or oral aciclovir has been described in patients with advanced HIV disease [13,14]. *In vitro* tests show that the virus isolated is deficient for thymidine kinase and therefore resistant to aciclovir. Famciclovir and valaciclovir are not active against VZV in this setting. Intravenous foscarnet is the agent of choice for aciclovir-resistant VZV infection [32,33].

6.2.6.4 Adjunctive therapy. There have been no studies of corticosteroids in the management of HIV-associated zoster and there is currently no indication they should be used. Likewise there are no specific studies addressing the management of postherpetic neuralgia in HIV-seropositive individuals. In the absence of these the therapeutic approach should follow that of HIV-seropositive individuals as outlined in recent guidelines [25].

6.2.7 Prophylaxis against varicella

Post exposure prophylaxis following significant exposure of an HIV-seropositive patient to VZV, and the potential use of the VZV vaccine in HIV-seropositive patients, are discussed in [34].

6.3 Herpes simplex virus (HSV) infection

6.3.1 Methods

The PubMed database was searched under the following headings: HIV or AIDS and herpes simplex virus or HSV or genital herpes or HSV encephalitis or HSV CNS disease.

6.3.2 Background and epidemiology

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are double-stranded DNA viruses of the *Herpesviridae* family. HSV infection most commonly causes genital or orolabial ulcerative disease. Genital HSV is the leading cause of genital ulcerative disease worldwide. Infection occurs from contact with infectious secretions on oral, genital or anal mucosa or abraded skin.

Following primary infection, HSV establishes viral latency in the cells of local sensory ganglia. Reactivation results in symptomatic clinical disease or asymptomatic viral shedding.

Some studies suggest the natural history of HSV in HIV-seropositive individuals is altered with reports of more severe clinical episodes of primary infection, and increased risk of symptomatic or more severe reactivation, in most studies, particularly in those involving individuals with more advanced HIV disease [35–38]. In addition individuals with lower CD4 counts or higher HIV viral loads are more likely to have recurrence of disease and to have HSV isolated from lesions or to shed virus asymptomatically [39,40]. There is, however, limited data and the exact consequences still require clarification.

The prevalence of HSV-1 and HSV-2 infections varies across different populations and is associated with several factors including age, gender, ethnicity and sexual behaviour. HSV-1 infection is largely acquired during childhood with prevalence rates rising to approximately 70% or higher in adults. HSV-2 is primarily sexually transmitted and prevalence steadily increases in adults with start of sexual activity in adolescence. HSV-2 infection is more common in HIV-seropositive than HIV-seronegative persons with prevalence rates of 60–90%, the highest rates being reported in sub-Saharan Africa [41,42]. The prevalence of HSV-2 infection in HIV-seropositive individuals in the UK has been reported as 63% and was associated with female gender, older age and black ethnicity [43].

There is an interaction between HSV and HIV infections, with evidence that genital HSV-2 infection increases acquisition risk of HIV and that co-infected individuals are more likely to transmit infection [44]. Genital herpes caused by HSV-2 infection has been shown to double the risk of becoming infected with HIV through sexual transmission [45]. HSV-2 has also been shown to increase the transmission of HIV, possibly due to high titres of HIV in genital secretions during HSV-2 reactivation [46].

6.3.3 Presentation

Orolabial herpes infection is most commonly caused by HSV type 1 and may involve the lips or the buccal and gingival mucosa. Intraoral ulceration usually indicates primary infection and is often associated with fever. Recurrent infection is usually limited to the lips. Typically, sensory prodromal symptoms of burning or tingling are rapidly followed by the development of vesicles that ulcerate and then crust over. Untreated lesions usually resolve within 7–10 days. Despite the

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observations above there is limited data on the impact of HIV infection on the clinical features of HSV-1 infection.

Primary genital herpes is defined as the first infection with either HSV-1 or HSV-2 in an individual with no pre-existing antibodies to either HSV type. Non-primary first episode genital herpes is defined as the first infection with either HSV-1 or HSV-2 in an individual with pre-existing antibodies to the other HSV type [47].

In individuals with reduced immune function, primary HSV may not resolve spontaneously but persist with the development of progressive, eruptive and coalescing mucocutaneous anogenital lesions [48–50]. In addition, healing of uncomplicated lesions may be delayed beyond 2–3 weeks, and is often associated with systemic symptoms such as fever and myalgia [51]. In rare cases, severe systemic complications, such as hepatitis, pneumonia, aseptic meningitis and autonomic neuropathy with urinary retention may develop and may be life-threatening.

In recurrent genital herpes, groups of vesicles or ulcers develop in a single anatomical dermatomal site and usually heal within 5–10 days. In HIV-seronegative persons, recurrences average five clinical episodes per year for the first two years and reduce in frequency thereafter. The frequency and severity of recurrent disease is significantly greater in HIV-infected persons with low CD4 cell counts [39,40]. HAART reduces the number of days with HSV lesions although it does not appear to normalize the frequency of reactivation to rates seen in HIV-seronegative individuals [52,53].

Atypical presentations of genital herpes have been reported in HIV-seropositive persons, including chronic erosive and chronic hypertrophic lesions in association with more severe immune deficiency, aciclovir resistance and starting HAART [53,54].

Nonmucosal or systemic HSV infection is more common and may be more severe in immunocompromised patients, though the clinical presentation may be similar to immunocompetent individuals [55]. HSV eye disease includes keratoconjunctivitis and acute retinal necrosis. Systemic HSV infection may result in pneumonia, hepatitis, oesophagitis and CNS disease. HSV infection of the CNS can cause aseptic meningitis, encephalitis, myelitis and radiculopathy. Preceding mucocutaneous disease is frequently absent. Aseptic meningitis is usually a consequence of primary HSV-2 infection and may be recurrent. HSV encephalitis has been reported in HIV-seropositive adults, but is uncommon. Clinical presentation includes fever, headache, decreased or fluctuating level of consciousness and seizures. Brainstem involvement may occur.

6.3.4 Diagnosis

6.3.4.1 Detection of HSV in clinical lesions (see Table 6.1). Swabs should be taken from the base of the lesion or fluid from the vesicle. For culture tests it is essential that the cold chain (4 °C) is maintained and appropriate media are used. PCR testing is most useful as less scrupulous handling of specimens is required [56]. PCR testing is rapid and sensitive resulting in increased identification of HSV-2 in lesions [57]. In one study the sensitivity of culture for HSV-2 was 73% as compared to 98% with PCR and both tests had 100% specificity [20].

Histopathology and PCR for HSV DNA may be helpful in the diagnosis of systemic disease. A positive PCR test must be interpreted in context with the clinical presentation and histology.

6.3.4.2 Serology. Commercial tests that use complement fixation are not type-specific. Seroconversion from a zero baseline is usually diagnostic of a primary infection. In the case of recurrent infection, an immune response from a non-zero baseline may be detected. However, these tests cannot distinguish between initial and recurrent infections and have been replaced by sensitive tests such as ELISAs and RIAs.

Type-specific serology tests (TSSTs) that detect HSV-specific glycoprotein G2, which is specific to HSV-2, and glycoprotein G1, which is specific to HSV-1 infection, are the only commercially available diagnostic tools to identify individuals with asymptomatic HSV infection, and can effectively distinguish HSV-1 and HSV-2 with high sensitivities (80–98%) and specificities ($\geq$96%) [58]. Case-controlled studies have shown that there are certain clinical situations where these tests may provide an aid to the diagnosis of HSV infection [59,60].

The clinical diagnosis of genital HSV infection has a low sensitivity and specificity; laboratory confirmation of infection and typing of HSV is essential as it influences the management, prognosis and counselling of patients.

6.3.4.3 CNS disease. In patients with HSV encephalitis or meningitis, typical CSF findings include a lymphocytosis and mildly elevated protein [61,62]. Low CSF glucose levels may also occur. Abnormal findings on magnetic resonance imaging and electroencephalogram are supportive of a diagnosis of HSV encephalitis but not diagnostic. For both HSV meningitis and encephalitis, PCR detection of HSV DNA in the CSF is the diagnostic method of choice and has a high specificity and sensitivity [62,63]. For HSV encephalitis, false-negative results for PCR may occur within the first 72 h of the illness and then 10–14 days after the onset of symptoms. Incidence of false-positive PCR is extremely low. Culture of the CSF for HSV is of little value in HSV encephalitis and not recommended.

- PCR for HSV DNA in the CSF is the diagnostic method of choice for diagnosis of HSV encephalitis or meningitis (category III recommendation).

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Table 6.1 Comparison of detection methods for HSV in clinical lesions [46,57,59].

	Tzanck smear	Virus culture	Antigen detection (DFA or EIA)	PCR
Sensitivity	Low	High	Low	Highest
Specificity	Low	High	High	High
Viral typing	No	Yes	No	Yes
Comments	Demonstrates giant cells from lesions. Provides presumptive evidence of infection.	'Gold standard'. Sensitivity declines as lesions heal.	Low cost and rapid.	Rapid but expensive. Useful in late clinical lesions. Test of choice in CSF examination. Used for research studies.

DFA, direct fluorescent antigen; EIA, enzyme immunoassay; PCR, polymerase chain reaction.

6.3.5 Treatment

6.3.5.1 Orolabial herpes

- First episode or severe recurrent orolabial herpes infection should be treated with antiviral therapy. Aciclovir 200–400 mg orally five times a day for 7–10 days is recommended (category II recommendation), Alternative treatments are valaciclovir or famciclovir. For severe oral mucocutaneous disease treatment should be initiated with aciclovir intravenously 5–10 mg/kg every 8 h (category III recommendation).

Most episodes of recurrent orolabial herpes are mild and self limiting. Episodic or suppressive antiviral therapy may be considered for those with severe or frequent recurrences. A study has shown equivalent efficacy of famciclovir 500 mg orally bd in comparison to aciclovir 400 mg orally five times a day in a mixed group of HIV-seropositive individuals with either orolabial (38%) or genital HSV [64]. There is not comparable data for the use of valaciclovir in treatment but on the basis of its activity in other settings and its efficacy in preventing recurrence of HSV in HIV-seropositive individuals [65] many clinicians would consider it as an alternative to aciclovir or famciclovir (category IV recommendation). Valaciclovir and famciclovir may be more expensive than aciclovir. There is no role for topical antiviral agents.

6.3.5.2 Genital herpes. The following recommendations for treatment of genital herpes are based on the BASHH and CDC guidelines for treatment of STIs in HIV-infected individuals All patients must receive information and support about their diagnosis and the clinician should document this and any issues arising from it. All patients should be strongly advised to inform a sexual partner about their infection [47,66].

6.3.5.2.1 First episode genital herpes

As for HIV-seronegative persons, the following general measures should be employed: cleaning of affected areas with normal saline; analgesia (systemic or local, e.g. lignocaine gel); and treatment of secondary bacterial infection.

- In view of the potential for more severe disease, prompt treatment with aciclovir 400 mg orally, five times daily for 7–10 days is recommended [64], (category II recommendation). Alternative regimens are valaciclovir 1 g orally twice daily for 5–10 days or famciclovir 250–750 mg orally three times daily for 10 days, but as above the recommendations for valaciclovir are extrapolated from other settings (category IV recommendation). In patients with severe cutaneous disease or systemic complications, aciclovir 5–10 mg/kg iv every 8 h should be considered (category III recommendation).

6.3.5.2.2 Recurrent genital herpes

Recurrent genital herpes in HIV-seropositive patients may be prolonged and more severe, however, most episodes are mild and self-limiting and can be managed with supportive and general measures only. The severity of recurrent episodes is reduced with immune reconstitution with HAART, although rates of genital HSV shedding are unchanged [52,67].

Suppressive antiviral therapy has been shown in meta-analyses of randomized controlled trials to significantly reduce (by 70–80%) the number of recurrences in patients with frequently recurring (more than six recurrences per year) genital herpes but the efficacy of this therapy in HIV-infected individuals appears to be less than that in HIV-negative individuals with one meta-analysis showing a 66% reduction in recurrences [68]. Individual randomised controlled trials have also demonstrated the efficacy of famciclovir and valaciclovir as suppressive agents in HIV-seropositive individuals [66,69,70].

- Recommended regimens for suppressive antiviral therapy include: aciclovir 400–800 mg orally two or three times a day (category Ia recommendation); valaciclovir 500 mg orally twice daily; or famciclovir 500 mg orally twice daily (category Ib recommendation)

Episodic antiviral therapy is also an option in patients who do not want to take regular suppressive therapy and who have a recognizable prodrome. The strategy has shown efficacy in HIV-seronegative individuals [71–73], though specific data

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from HIV-seropositive individuals is more limited. Antiviral therapy should be initiated during the prodrome or early in an attack and aciclovir 200–400 mg orally five times daily for 5 days is recommended [47]. Alternative regimens are aciclovir 400 mg orally three times a day for 5 days; valaciclovir 500 mg orally twice daily for 3–5 days; valaciclovir 1 g orally, twice daily for 5 days; famciclovir 500 mg orally twice daily for 5 days. There is no evidence of clear superiority of the alternative regimens over standard doses of aciclovir.

In more immunocompromised HIV-seropositive persons, episodes may be prolonged and more severe, requiring a longer duration of antiviral treatment.

In HIV negative individuals, discontinuation of suppressive or episodic antiviral therapy after 12 months is recommended in order to assess the ongoing frequency of recurrences. In an HIV-seropositive individual with a low CD4 cell count, the interruption may be delayed. The timing of this treatment interruption should be agreed with the patient and they should be given a supply of antiviral therapy to enable prompt administration of episodic treatment if recurrences recur.

6.3.5.3 Non-mucosal (or systemic) herpes. There is limited data on the treatment of systemic HSV disease in HIV-seropositive individuals. Recommendations are based on evidence from studies in both immunocompetent and immunocompromised patient populations.

Systemic infection should be treated with intravenous aciclovir 5–10 mg/kg every 8 h for 10–21 days. HSV meningitis can be treated with 10 mg/kg every 8 h [74].

For HSV encephalitis, aciclovir 10 mg/kg every 8 h for 14–21 days is recommended [75] and quantitative PCR in the CSF may be helpful in monitoring response to treatment. Mortality and morbidity is high. Joint care with a neurologist is essential and there should be a low threshold for referral to a brain ITU.

Patients with HSV keratoconjunctivitis or acute retinal necrosis should be seen urgently by an ophthalmologist and managed jointly.

6.3.5.4 Antiviral-resistant HSV infection. In prospective studies, aciclovir-resistant HSV variants have been described in up to 7% of isolates from HIV-seropositive patients [76,77]. The threshold for resistance is a greater than 1–3 mg/mL aciclovir concentration for viral inhibition. This is most usually due to a mutation affecting the gene encoding viral thymidine kinase (TK), the enzyme that phosphorylates aciclovir in HSV-infected cells. TK-deficient strains are of reduced pathogenesis in immunocompetent individuals but cause significant clinical disease in immunosuppressed patients.

Although partial resistance can occur, most TK mutants are resistant to aciclovir, valaciclovir and ganciclovir and the majority to famciclovir. However, foscarnet and cidofovir therapy do not require TK-dependent phosphorylation but directly inhibit viral DNA polymerase.

- Any immunocompromised HIV patient developing clinical HSV lesions despite adequate doses of aciclovir, valaciclovir or famciclovir must have a sample taken for viral culture and testing for antiviral sensitivity. If new lesions are forming after 5 days, despite increasing the doses of antiviral drugs then therapy should be reviewed and changed (category IV recommendation).

Topical 1% foscarnet cream or 1% cidofovir gel have been reported to increase lesion healing, reduce symptom score and virological effect [78–80]. In the UK 1% foscarnet cream is not commercially available; however, a 2% formulation is available from Idis Pharmaceuticals.

Systemic therapy with either iv foscarnet 40 mg/kg bd or tid iv has been shown to be effective for aciclovir resistant strains with the length of therapy depending on treatment response [81] and [82], (category Ib recommendation). In rare cases with aciclovir and foscarnet resistance cidofovir topically [83] or iv 5 mg/kg weekly infusion is the preferred agent [84] (category III recommendation).

6.3.6 Antiretroviral therapy

In patients with prolonged cutaneous ulceration or who have systemic disease, consideration should be given to initiating combination antiretroviral therapy or changing therapy in those experiencing virological failure [category IV recommendation].

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7 Candidiasis

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Keywords: candidiasis, *Candida albicans*, non-albicans Candida, oesophagitis

7.1 Methods

The PubMed database was searched under the following headings: HIV or AIDS and candidosis, candidiasis, *Candida* spp, *Candida albicans*, non-albicans Candida, oropharyngeal candidiasis and mucosal candidiasis.

7.2 Background and epidemiology

Candida species are common commensals in the general population and may be cultured using selective media from the oral cavity and genital tracts of up to 75% of individuals [1]. Such cultures are not clinically helpful. Oropharyngeal candidiasis is the commonest opportunistic infection to affect HIV-seropositive individuals, occurring in 80–90% of patients in the pre-HAART era [2]. Oesophageal candidiasis in the pre-HAART era was the AIDS-defining illness in 11% of cases [3].

7.3 Presentation

Oral candidiasis is associated with worsening immunodeficiency [4] and in the absence of HAART predicts the development of AIDS at a median of 25 months [5]. The most familiar clinical appearance of oral candidiasis is of easily removable curdy white plaques, underneath which lies raw or bleeding mucosa. Other presentations include an erythematous form, with patchy reddening of the mucosa, and depapillation of the dorsal surface of the tongue [6]; hyperplastic candidiasis, where there are white plaques that cannot be scraped away; and angular cheilitis with painful fissuring of the commissures. The symptoms are of pain in the tongue or surrounding structures or the presentation may be asymptomatic with just the clinical appearance of oral candidiasis.

Vaginal candidiasis is common in HIV-seropositive women and presents with vaginitis with itching and curd-like exudate. Management is as for HIV-seronegative individuals [7].

Typically the patient with oesophageal candidiasis complains of dysphagia and/or odynophagia. Oesophageal candidiasis without oral evidence of plaques is infrequent and where a patient complains of typical symptoms in the absence of oral candidiasis other diagnoses must be considered. However, in a minority of cases oesophageal candidiasis may occur without oral involvement [8].

Invasive candidiasis is seen in more immunocompromised patients, in particular those with central venous catheters, prolonged antimicrobial usage or intensive care unit admission.

7.4 Diagnosis

- Oral and oesophageal candidiasis are clinical diagnoses (category IV recommendation).
- Microbiological confirmation and susceptibility testing of *Candida* spp is required when symptoms of candidiasis persist or develop whilst the patient is taking antifungal therapy (category IV recommendation).

Oral and oesophageal candidiasis are clinical diagnoses, and microbiological confirmation is not advised due to the likelihood of positive cultures in the absence of clinical disease. *Candida* cultures should be requested only for studies of resistance in individuals not responding to standard therapy. *C. krusei* is always fluconazole-resistant, and may be cross-resistant to itraconazole and ketoconazole. *C. glabrata* sensitivity is more variable with many strains showing fluconazole resistance [9]. Susceptibility testing is recommended for patients with clinical disease from whom these species are isolated and for cases in which there is a slow response to therapy or development of candidiasis despite azole therapy for some other reason.

- Oesophageal candidiasis can be diagnosed clinically if oropharyngeal candidiasis is present (category IV recommendation).
- Confirmation by endoscopy can be reserved for cases with symptoms of oesophageal candidiasis who fail to respond to initial therapy, do not have concomitant oropharyngeal candidiasis or those in which an additional oesophageal condition is suspected (category IIb recommendation).

Endoscopy should reveal white patches. The main value of endoscopy is to exclude other causes of oesophageal symptoms that may be present with or without oesophageal candidiasis or obtain samples for susceptibility testing if response to therapy is not detected.

7.5 Treatment

- Azoles and topical treatment are equally effective at treating oropharyngeal candidiasis but azole therapy is

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associated with a lower risk of relapse (category Ib recommendation).

Azoles are the mainstay of treatment for HIV-seropositive patients with oral or oesophageal candidiasis. Topical nystatin or amphotericin are of little benefit for oesophageal candidiasis, and although as effective as azoles for oropharyngeal candidiasis, are associated with slower clearance of yeast from the mouth and a higher relapse rate [10].

Fluconazole (50–100 mg/day), ketoconazole (200 mg bd) and itraconazole (200 mg od) are the most commonly selected orally absorbable systemic azoles, and all have efficacy against oropharyngeal candidiasis when prescribed for 7–14 days [11–16]. Fluconazole is most often recommended. Itraconazole may be used in select cases when fluconazole resistance has been demonstrated. Ketoconazole is mainly of historical interest. Studies have suggested greater efficacy with fluconazole and oral solution of itraconazole than with ketoconazole or itraconazole tablets [11,16,17]. Both fluconazole and itraconazole have demonstrated efficacy in the treatment of oesophageal candidiasis with fluconazole providing greater short-term response [18].

Ketoconazole and itraconazole capsules require gastric acid to facilitate absorption, and achlorhydria, which is associated with advanced HIV disease, will impair the efficacy of these agents [19,20]. Itraconazole oral solution shows better bioavailability [17]. Patients with low CD4 T-cell counts are thus best treated with fluconazole, as are those requiring systemic antacid preparations.

Ketoconazole and itraconazole are metabolized via cytochrome P450 enzymes and therefore should not be co-prescribed with hepatic enzyme-inducing agents such as rifamycins. Fluconazole is excreted predominantly unchanged in the urine and is therefore the azole of choice in patients requiring treatment with such enzyme inducers. It is advisable to use fluconazole, as the least hepatotoxic agent, in patients with liver disease. Ketoconazole is teratogenic in laboratory animals, is contraindicated in pregnancy and like other azoles can cause hepatitis [21].

Individuals with fluconazole-refractory candida may respond to itraconazole cyclodextrin (oral) solution 200 mg bd [22,23]. Where this is not possible, clotrimazole pessaries (100 mg) have been used orally (sucked rather than swallowed) or clotrimazole troches (10 mg), available in the US, may be effective (Cartledge JD, personal communication). Alternatively amphotericin B oral solution or lozenges may be used [24]. In patients with severe oesophageal symptoms, or those with severe oropharyngeal candidiasis who do not respond to itraconazole solution or clotrimazole cloches, or those with strains with elevated minimum inhibitory concentration (MIC) to fluconazole and itraconazole intravenous therapy with amphotericin B, echinocandins or newer azoles may be effective.

- Voriconazole, posaconazole or the echinocandins (caspofungin, micafungin and anidulafungin) should be reserved for cases in which the organism is resistant to fluconazole but sensitive to the newer agent, to cases which fail to respond clinically to fluconazole despite sensitivity or where the individual is intolerant of fluconazole therapy (category IV recommendation).

There are a number of antifungal drugs that can be considered for the treatment of fluconazole-refractory disease [25]. These include the azoles, voriconazole and posaconazole, and the echinocandins, caspofungin, micafungin and anidulafungin, which have shown efficacy in randomized clinical trials against oesophageal candidiasis although cost means their use should be reserved for cases where traditional fluconazole therapy is ineffective, not tolerated or where infection is due to organisms with altered susceptibility to first-line agents. In clinical trials of oesophageal candidiasis caspofungin was as effective but less toxic than amphotericin B [26] and was active against fluconazole-resistant strains [27]. Caspofungin, micafungin and anidulafungin have shown efficacy comparable to fluconazole in treatment of oesophageal candidiasis [28–30]. Only micafungin has resulted in a relapse rate comparable to fluconazole; caspofungin shows a trend towards, and anidulafungin is associated with a significantly higher relapse rate [26,29,30]. However, interpretation of these differences is hampered by the different doses of fluconazole used in the different studies [25]. Voriconazole is also active against resistant strains [31] and was as effective but more toxic than fluconazole [32], and posaconazole also showed efficacy against oropharyngeal/oesophageal candidiasis [33], including candidiasis refractory to fluconazole/itraconazole [34].

There are no clinical trial data to guide the treatment of invasive candidiasis in HIV-seropositive individuals. In general, they should be treated with systemic antifungal therapy as in other immunocompromised patients (category IV recommendation). The British Society for Medical Mycology has published proposed standards of care for invasive fungal infections, including *Candida* [35].

7.6 Prophylaxis

- Routine prophylaxis is not warranted and is associated with the emergence of resistance (category III recommendation).

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Table 7.1 Candida infection treatment and antiretroviral drug interactions

Drug name	Interaction with antiretroviral	Action required
Antifungals		
Amphotericin	Tenofovir	Caution – increased risk of renal toxicity with concurrent or recent use.
Itraconazole	Ritonavir increases itraconazole exposure	Avoid high doses of itraconazole
		Caution with boosted PIs – some PI levels increased
	Efavirenz, etravirine and nevirapine reduce itraconazole levels	Consider alternative, or increase dose
		Monitor clinical effect
	Maraviroc levels increased	Reduce maraviroc dose (150 mg bd)
Voriconazole	Efavirenz levels increased and voriconazole levels reduced	Not recommended to be used together. Seek HIV specialist pharmacist advice
	Etravirine and voriconazole levels are both increased	No dose adjustment required – monitor
	Lopinavir/ritonavir reduces voriconazole levels	Not recommended to be used together. Seek HIV specialist pharmacist advice
Fluconazole	Zidovudine levels increased	Caution – monitor for adverse effects
	Nevirapine levels increased	Caution – monitor for adverse effects
Posaconazole	Efavirenz reduces posaconazole levels	Avoid combination unless benefit to patient outweighs risk
	Atazanavir levels increased	Caution – additional monitoring for toxicity (bilirubin levels)
	Other PIs – levels possibly increased	Monitor for signs of increased toxicity
Caspofungin	Efavirenz and nevirapine reduce levels.	Increase caspofungin dose to 70 mg od, for those <80 kg

Antiretroviral drugs, especially the NNRTIs and boosted PIs, have several important drug–drug interactions. This table lists some examples of drug–drug interactions with antiretrovirals and antifungals. As the azole antifungal compounds are metabolized via the cytochrome P450 enzyme system they are likely to interact with both NNRTIs and PIs. There are few published data on potential drug interactions with the newer antifungal agents. As data and advice changes frequently, this information should always be interpreted in conjunction with the manufacturer's information (www.medicines.org.uk). Other useful web-based reference sources include the Liverpool HIV drug information website (www.hiv-druginteractions.org) and the Toronto Clinic (www.hivclinic.ca/main/drugs_interact.html).

Ongoing prescription of azole antifungals between episodes of recurrent candidiasis is not recommended as this is associated with emergence of azole-resistant candidiasis [36–38]. In the pre-HAART era, azole-unresponsive candidiasis was increasingly common in patients who had received prolonged prophylaxis with azole antifungals, and was either due to infection with species other than *C. albicans* [39–41], such as *C. krusei* and *C. glabrata*, or resistant strains of *C. albicans* [42–45].

7.7 Impact of HAART

As with other opportunistic infections, effective antiretroviral therapy prevents relapses of symptomatic candidiasis. Thus the most successful strategy for managing patients with candidiasis is HAART (see Table 7.1). There are rare reports of candidiasis associated with IRIS, including a case of *Candida* meningitis leading to fatal vasculitis [46].

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8 *Mycobacterium avium* complex and *Mycobacterium kansasii*

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Keywords: *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*

8.1 Methods

The PubMed database was searched under the following heading: HIV or AIDS and atypical mycobacterial infections, *Mycobacterium avium* complex or *Mycobacterium avium intracellulare* and *M. kansasii*.

8.2 Introduction

Many atypical mycobacteria have been reported to be isolated and/or cause disease in patients with HIV infection. This is typically in the context of very advanced immunosuppression (CD4 counts of <50 cells/μL) and with most patients having disseminated focal disease. The commonest of these infections are *M. avium* complex (MAC) and *M. kansasii*.

Since these organisms are frequently commensals from multiple environmental sources, it is important that a clinical decision is made that the organism is considered to be the cause of disease rather than an incidental finding prior to any specific treatment initiation.

With the exception of MAC, there is limited evidence to guide decisions of choice or duration of therapy and expert opinion should be sought from a clinician experienced in mycobacterial disease. Most of the recommendations for the treatment of atypical mycobacteria have been extrapolated from trials in HIV-seronegative individuals. Where an individual is markedly immunosuppressed, some physicians may increase the number of antimycobacterial agents and/or the duration of therapy.

8.3 *Mycobacterium avium* complex

8.3.1 Background and epidemiology

Mycobacterium avium complex (MAC) organisms are present throughout the environment. *Mycobacterium avium* is the predominant atypical mycobacterium that affects patients with HIV-1. Infection occurs via the respiratory or gastrointestinal tracts. No particular activity is known to predispose to infection, and person-to-person transmission is not believed to occur.

Prior to the advent of HAART, disseminated MAC was seen in 40% of patients with advanced HIV infection [1], with even higher rates at autopsy [2]. Since the start of the widespread use of HAART, the incidence of MAC has reduced significantly [3] and the prognosis has improved markedly [4], although the clinical picture has changed to include immune reconstitution disease [5] and focal infection.

8.3.2 Presentation

Disseminated MAC infection (DMAC) typically occurs in patients with advanced immunosuppression who have CD4 counts <50 cells/μL. Patients with DMAC frequently have nonspecific symptoms, signs and laboratory abnormalities, which may be attributed incorrectly to HIV progression or other HIV-related illnesses. Patients most commonly report fever, night sweats, fatigue, weight loss, anorexia and diarrhoea. Common signs include hepatomegaly and lymphadenopathy while laboratory abnormalities include anaemia, leukopenia, elevated alkaline phosphatase levels and hypoalbuminaemia. Radiological features include hepatosplenomegaly and intra-abdominal lymphadenopathy, which were demonstrated in one case series using abdominal computed tomography (CT) in 14 of 17 patients with DMAC [6]. More unusual focal manifestations of MAC infection include palatal and gingival ulceration, septic arthritis and osteomyelitis, endophthalmitis, pericarditis, pulmonary and focal lymphadenitis [4,7–10].

8.3.3 Diagnosis

- Diagnosis of DMAC requires culture in blood or from a bone marrow aspirate or fluid from a normally sterile site or biopsy specimen (category III recommendation).
- Culture of MAC from sputum or stool in the absence of other proof of DMAC is insufficient diagnostic evidence (category III recommendation).

Definitive diagnosis of DMAC requires culture of the organism from a sterile body site. Isolation of MAC from non-sterile sites (sputum or stools) in the absence of clinical/radiological features suggestive of disseminated infection is insufficient to warrant antimycobacterial therapy. In some situations empirical treatment may be considered pending the results of culture given the time period necessary before cultures can be reliably deemed negative.

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Mycobacterial blood culture (standard and liquid) establishes the diagnosis in 86–98% of cases in which disseminated MAC infection is confirmed at autopsy [11,12]. One blood culture identifies 91% of patients with MAC bacteraemia, a second blood culture increases the identification rate to 98% [13]. Therefore, obtaining paired or more than two sequential blood specimens for culture to diagnose MAC bacteraemia is unnecessary [14].

The preferred culture method includes lysis of peripheral blood leukocytes to release intracellular mycobacteria followed by inoculation on to solid media (e.g. Lowenstein–Jensen, Middlebrook 7H11 agar) or into radiometric broth [15]. Using the radiometric detection system, mycobacteraemia can be detected in as little as 6–12 days, whereas 15–40 days are required with solid media. In addition, DNA probes can identify MAC species within 2 h once sufficient mycobacterial growth has occurred in radiometric broth or on solid media [16]. Multiplex PCR have also been shown to provide a low-cost alternative to DNA probe methods for rapid identification of MAC [17].

Biopsies from other normally sterile body sites can prove diagnostic. Stains of biopsy specimens from bone marrow, lymph node or liver may demonstrate acid-fast organisms or granulomata weeks before positive blood culture results are obtained [18,19].

8.3.4 Treatment

8.3.4.1 Treatment regimens for DMAC

- Antimycobacterial treatment of DMAC requires combination therapy that should include a macrolide and ethambutol, with or without rifabutin (category Ib recommendation).
- Addition of rifabutin should be considered in cases with advanced immunosuppression, marked symptoms or an inability to construct an effective HAART regimen (category III recommendation).
- Treatment failure is usually addressed with a combination of at least two new drugs including fluoroquinolones, amikacin and other agents (category III recommendation).
- Treatment should be continued until there is an adequate immunological response to HAART or in the absence of this life-long (category III recommendation)

Macrolide-containing regimens are associated with superior clinical outcomes in randomized clinical trials as compared to non-macrolide-containing regimens [20] (category Ib recommendation). Clarithromycin and azithromycin have both demonstrated clinical and microbiological activity in a number of studies; however, macrolide monotherapy is associated with rapid emergence of resistance [21]. Clarithromycin has been studied more extensively than azithromycin and is associated with more rapid clearance of MAC from the blood [22,23]. However, azithromycin has fewer drug interactions and is better tolerated [24]. The dose of clarithromycin should not exceed 500 mg bd as higher doses have been associated with excess mortality [25]. Emergence of macrolide resistance is associated with a return of clinical symptoms and/or increased bacterial counts in some patients [21]. Therefore, addition of at least one further class is recommended.

Ethambutol is the most commonly recommended second drug [25] and its addition to combinations used for MAC treatment reduces the development of macrolide resistance [26,27]. Ethambutol does not interact with currently available antiretroviral agents. A third drug (usually rifabutin) may be included in the regimen. One randomized clinical trial demonstrated that the addition of rifabutin to the combination of clarithromycin and ethambutol improved survival and the chance of complete microbiological response during the study period, though not microbiological clearance at the primary end-point of 12 weeks or relapse rate, while another study showed it reduced emergence of drug resistance [28,29]. Rifabutin dosage should not exceed 300 mg/day (or 450 mg if given with efavirenz or 150 mg three times a week if given with ritonavir) as cases of uveitis have been reported with higher doses, especially when given with clarithromycin [30–32]. It should be noted that many of the benefits of rifabutin were described pre-HAART and the benefits may be more marginal if HAART is administered. Significant drug–drug interactions also exist between rifabutin and antiretroviral agents (protease inhibitors and NNRTIs), which will affect the decision of whether to use rifabutin as a third agent and/or whether to modify the choice of HAART regimen (see Table 8.1). In situations where there is a high risk of short-term mortality the addition of rifabutin should be strongly considered, for instance in persons with:

(1) Advanced immunosuppression ($CD4^+$ T lymphocyte count <25 cells/μL);
(2) Markedly symptomatic DMAC features and/or laboratory parameters (as described above);
(3) A situation where there is an inability to construct an effective HAART regimen.

There are few supporting data for the use of other drugs such as a fluoroquinolones or parenteral amikacin [33]. These should therefore only be considered when rifabutin or other first-line drugs cannot be used because of drug interactions, intolerance or treatment failure. Clofazimine should not be used in the treatment of MAC as it is associated with excessive toxicity and higher mortality rates [34].

In summary, the preferred regimen for disseminated MAC is clarithromycin (500 mg twice daily) or azithromycin

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Table 8.1 Potential atypical mycobacterial infection treatment and antiretroviral drug interactions

Drug name	Interaction with antiretroviral	Action required
Antibiotics		
Clarithromycin	NNRTIs, PIs and boosted PIs can alter clarithromycin levels	See individual antiretroviral manufacturer's information
	Zidovudine levels may be decreased	Separate dose interval by 1–2 h
	Maraviroc likely to be increased	Reduce dose of maraviroc (150 mg od)
Rifabutin	Boosted PIs increase rifabutin levels	Reduce rifabutin dose (150 mg three times weekly)
	Unboosted PIs increase rifabutin levels	Reduce rifabutin dose to 150 mg od
	Indinavir and saquinavir should not be used with rifabutin	
	Efavirenz reduced	Consider increasing rifabutin dose (450 mg od)
	Etravirine – limited data	Use with caution (standard 300 mg od)
		Levels decreased when used in conjunction with a boosted PI
Rifampicin	NNRTI levels reduced	Increase dose of efavirenz (800 mg od) depending on patient's weight)
		Contraindicated with etravirine and nevirapine (some units increase nevirapine dose)
	PI levels significantly reduced	Not recommended to be used together. Seek HIV specialist pharmacist advice
	Maraviroc levels reduced	Increase maraviroc dose (600 mg bd)
	Raltegravir levels reduced	Consider increasing dose of raltegravir (800 mg bd)

Antiretroviral drugs, especially the NNRTIs and boosted PIs, have several important drug–drug interactions. This table lists some examples of drug–drug interactions with antiretroviral agents and drugs used in atypical mycobacterial infections. As data and advice changes frequently, this information should always be interpreted in conjunction with the manufacturer's information (www.medicines.org.uk). Other useful web-based reference sources include the Liverpool HIV drug information website (www.hiv-druginteractions.org) and the Toronto Clinic (www.hivclinic.ca/main/drugs_interact.html).

(500 mg/day) plus ethambutol (15 mg/kg/day). If rifabutin (usually 300 mg/day) is included in the regimen a dose adjustment is necessary if concurrently administered with a ritonavir-boosted protease inhibitor (150 mg three times a week) or efavirenz (450 mg daily) (*see* Table 8.1).

8.3.4.2 Length of treatment for DMAC

- Individuals receiving HAART with a virological response and a CD4 count >100 cells/μL for at least 3 months in whom there has been a clinical response to DMAC therapy for at least 3 months can discontinue therapy (category 3 recommendation)

Most studies of the treatment of DMAC were performed in the pre-HAART era. However, there is no doubt that one of the most effective treatments for DMAC is HAART. HAART should be initiated simultaneously or within 1–2 weeks of initiation of antimycobacterial therapy for DMAC disease, based on the experience with a range of opportunistic infections including a small number of cases with MAC [35] (category IV recommendation). If patients are already on HAART at the time of DMAC diagnosis, HAART should be continued and/or adjusted to ensure the viral load is undetectable (<50 copies/mL HIV-1 RNA) (category IV recommendation). Successful initiation of HAART is a key determinant of the duration of DMAC therapy.

The incidence of DMAC has dropped dramatically with the use of HAART. Prior to the HAART era, therapy for DMAC was life-long. It has become clear that immune reconstitution and CD4 cell recovery secondary to HAART enables successful withdrawal of MAC therapy in most cases.

Whilst there are no randomized clinical trial data to strongly recommend duration of MAC therapy after initiation of HAART, prospective non-randomized studies [36,37] and cohort studies [38,39] would suggest DMAC therapy can be safely discontinued in patients responding to HAART. Although studies have differed with regard to the exact conditions that need to be fulfilled before DMAC therapy is stopped, the minimal conditions that should be satisfied are a clinical response to MAC therapy for at least 3 months' duration (asymptomatic with negative blood cultures after 6 weeks incubation) and both of the following:

(1) virological response to HAART (viral load <50 copies/mL on two consecutive occasions); and
(2) an immunological response to HAART (confirmed CD4 count >100 cells/μL) on two separate occasions at least 3 months apart.

In the absence of these criteria being met DMAC treatment should be continued lifelong or until these criteria can be met.

8.3.4.3 Treatment failure for DMAC. Patients are considered to have treatment failure if there is no clinical response and mycobacteria are isolated from cultures after 4–8 weeks of MAC treatment to which the patient has been adherent. Drug susceptibility testing is of limited use for agents other than macrolides (category III recommendation). Ethambutol and rifabutin drug susceptibility to MAC has not been correlated to clinical response to therapy although there are data for clarithromycin and azithromycin [40,41]. A new combination of at least two drugs not previously used and to which the isolate should

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be susceptible should be constructed (category III recommendation) – e.g. rifabutin (if not used previously), ciprofloxacin, levofloxacin, ofloxacin or moxifloxacin [42], linezolid or amikacin. Other second-line agents (such as ethionamide, prothionamide or cycloserine) have been used anecdotally. Many clinicians would continue ethambutol since it facilitates the penetration of other agents into mycobacteria (category IV recommendation).

Immunomodulators, including granulocyte colony-stimulating factor and interferon gamma, can be considered in cases of DMAC treatment failure. They are thought to work by inhibiting intracellular replication or enhancing *in vitro* intracellular killing of *M. avium* but there are no comprehensive studies of these agents [43,44].

8.3.4.4 Treatment of focal MAC. There are no data to guide the type or duration of therapy for focal MAC. However, given that these tend to occur at higher CD4 cell counts and in the presence of effective HAART, most clinicians would recommend a three-drug regimen for a duration of at least 12 and possibly 24 months.

Potential drug interactions may lead to modifications in the HAART and/or antimycobacterial regimen (*see* Table 8.1).

8.3.5 Primary prophylaxis

- Prophylaxis for DMAC with azithromycin 1250 mg weekly can be considered for individuals with CD4 counts <50 cells/μL (category Ib recommendation).
- Primary prophylaxis can be stopped in the presence of a virological response to HAART (viral load <50 copies per mL) and a CD4 count >50 cells/μL for at least 3 months (category III recommendation).

Randomized clinical trials have demonstrated a benefit of clarithromycin/azithromycin or combinations of rifabutin and azithromycin [45,46] in reducing the incidence of MAC infection in patients with a CD4 count of <100 cells/μL. However, these studies were conducted prior to the introduction of HAART, which has itself resulted in a massive reduction in the incidence of MAC [3]. Furthermore, in one of these studies, where CD4 cell counts at diagnosis of DMAC were provided, it was observed that no cases of DMAC occurred with a CD4 count >50 cells/μL. Thus, lowering the CD4 count at which primary prophylaxis should be considered to <50 cells/μL is recommended in line with many other guidelines. It is therefore recommended that MAC prophylaxis *should* be considered for individuals with a CD4 count of <50 cells/μL who are either not accepting HAART or who are experiencing HAART failure (category Ib recommendation).

In such individuals, the decision to recommend MAC prophylaxis will need to balance the potential clinical benefits against the additional pill burden, possible added drug-related toxicity, and risk of resistance if undiagnosed DMAC is present (category IV recommendation).

Rifabutin, clarithromycin or azithromycin are acceptable, although azithromycin (1250 mg weekly) is preferred since it has fewer potential drug–drug interactions and is better tolerated (category Ib recommendation). The dose recommended in this guideline differs from the 1200 mg dose traditionally recommended in other guidelines and reflects the size of azithromycin tablets available in the UK.

Primary prophylaxis can be stopped when the patient has a response to HAART (viral load <50 copies per mL) and a CD4 count >50 cells/μL for at least 3 months (category III recommendation). Some physicians prefer to use a cut-off of 100 cells/μL based on evidence from two papers. In these studies, all the patients had CD4 counts >100 cells/μL on stopping prophylaxis, but no cases of DMAC and only two cases of atypical focal MAC were seen [47,48]. No data are available for a >50 cells/μL cut-off. However, owing to the effect of antiviral therapy on MAC, the toxicity of azithromycin seen in prophylaxis studies, and the fact that almost all cases of MAC occur at CD4 counts of less than 50 cells/μL, as evidenced in the Pierce study [46], a cut-off of 50 cells/μL has been considered most appropriate.

8.3.6 Impact of HAART

- HAART should be commenced within 2 weeks of starting MAC therapy (category IV recommendation).

The incidence of DMAC has dropped dramatically with the use of HAART. HAART should be initiated promptly after diagnosis of MAC and primary and secondary prophylaxis can be discontinued after an initial response to HAART as outlined above.

MAC IRIS can occur as focal disease presenting as regional lymphadenopathy, liver lesions, bone lesions or hypercalcaemia [49–54]. This syndrome is usually self-limiting but can be severe and require adjunctive therapy. There are currently no randomized data to recommend the optimal management strategy. However, the following have been used with anecdotal benefit (category III recommendation) and may be considered in select cases:

(1) Corticosteroid therapy, with 20–40 mg of oral prednisolone a day for 4–8 weeks has been most frequently used;
(2) IL-2 and GM-CSF have been used successfully in a small number of patients [55];
(3) Leukotriene inhibitors have been used in TB-associated IRIS in cases refractory/intolerant to steroids [56,57];
(4) Repeated fine-gauge needle aspiration of pus, as used with lymphadenitis due to *Mycobacterium tuberculosis*.

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8.4 *Mycobacterium kansasii*

8.4.1 Background and epidemiology

M. kansasii is the second most common nontuberculous mycobacterium producing disease in patients with HIV infection [58].

Pulmonary disease is seen in over half of patients [58–60], and bacteraemia occurs in fewer than 25% of individuals, although disseminated infection is associated with advanced immunosuppression.

8.4.2 Presentation

Presentation is pulmonary in over half of cases [59–61]. The most typical presenting symptoms/features are fever, cough, focal pulmonary signs on examination and radiological features of pulmonary cavities or infiltrates. Approximately 10% of cases may have mycobacteraemia [62].

8.4.3 Diagnosis

Since *M. kansasii* may be a commensal organism, diagnosis requires both repeated isolation and a compatible clinical and radiological picture (category IV recommendation).

8.4.4 Treatment

- Where clinically indicated, treatment is with rifamycin + ethambutol + isoniazid for a minimum of 12 months (category IV recommendation).

The decision to initiate therapy must be clinically based. In patients where *M. kansasii* is isolated from non-sterile sites (usually sputum) in the absence of clinical and or radiological disease, specific therapy should be withheld. Repeated positive isolates may signify active disease even in the absence of new symptoms.

Therapy should be with a rifamycin such as rifampicin 600 mg od or rifabutin 300 mg od plus ethambutol 15 mg/kg with high-dose isoniazid 300 mg od plus pyridoxine 20 mg od for at least 12 months (category IV recommendation) and possibly for at least 12 months of documented sputum negativity. However, the duration is based on pre-HAART and/or HIV-seronegative extrapolation data (for more details see [63]). There is also experience with the combination of clarithromycin, rifampicin and ethambutol (category IV recommendation).

The treatment regimen for disseminated disease should be the same as for pulmonary disease. Because of the critically important role of rifamycins in the treatment of *M. kansasii* disease, it is important to construct *M. kansasii* and antiretroviral treatment regimens that are compatible (see Table 8.1). The recommended regimen for *M. kansasii* would be rifampicin/rifabutin plus ethambutol plus/minus high-dose isoniazid. An option for treating HIV-seropositive patients who receive an antiretroviral regimen not compatible with rifamycins is to substitute a macrolide or quinolone (e.g. ofloxacin) for the rifamycin. The recommendations for duration of therapy for disseminated *M. kansasii* disease in patients with HIV are similar to the recommendation for duration of therapy for disseminated MAC infection (above).

8.4.5 Prophylaxis

There is no recommended prophylaxis, and secondary prophylaxis is not indicated for disseminated *M. kansasii* disease as is the case with *M. tuberculosis*.

8.4.6 Impact of HAART

There is insufficient data to allow comments on the impact of HAART.

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9 Pyrexia of unknown origin (PUO)

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9.1 Background

General review definition divides PUO as classical, nosocomial, HIV-related and immunosuppression-related [1]. For HIV infection, pyrexia of unknown origin (PUO) identifies a pattern of fever with temperature higher than 38.3 °C on several occasions over more than 4 weeks for outpatients, or more than 3 days duration in hospital, in which the diagnosis remains uncertain after an initial diagnostic work-up, including at least 2 days of incubation of microbiological cultures [2]. It is a common clinical manifestation in HIV-seropositive patients with severe immunosuppression and probability of an infection-related aetiology for PUO in HIV infection increases with CD4 decline, i.e. greater risk if CD4 count <50 cells/μL than <100 cells/μL than >200 cells/μL [3].

- Fever is rarely the result of the effects of HIV itself and investigation of a specific cause should be actively pursued [4] (level of evidence IV).

Causes of PUO in cohorts of HIV-seropositive patients vary between published studies and are influenced by diagnostic criteria used, degree of immunosuppression, risk category for HIV infection and geographical location of cohort. Comparison of causes of PUO in HIV-seropositive to seronegative patients shows that infection is the most frequent cause of PUO in patients with HIV infection whilst collagen diseases are more common in patients without HIV infection [5].

Many studies were performed before the widespread availability of antiretroviral therapy where the majority of patients had a very low CD4 cell count. The main causes of PUO in patients with severe immunodeficiency are infections and lymphoma [4,6]. Furthermore, these patients often have multiple diagnoses [6,7].

- Multiple diagnoses are common, and should be considered in all persons with severe immunosuppression (level of evidence III).

A careful travel history is paramount. The commonest cause of PUO in a study from USA was disseminated *Mycobacterium avium* infection (DMAC) [6] whereas reports from southern Europe and Brazil have described disproportionately more cases of leishmania species or *Mycobacterium tuberculosis* [8,9]. Febrile illnesses are well described presentations in both disseminated histoplasmosis [10] and *Penicillium marneffei* [7,11] in persons who have travelled to or originated from an endemic area.

- Take a careful history, including a lifetime travel history, as new and reactivation of tropical infections are not uncommon (level of evidence IV).

In the era of HAART, tuberculosis and lymphoma continue to be significant causes of PUO. However, as the HIV-seropositive population ages due to the success of HAART, multisystem diseases (encompassing rheumatic diseases, connective tissue disorders, vasculitis including temporal arteritis, polymyalgia rheumatica, and sarcoidosis) should be considered in the differential diagnosis [12].

PUO may present as a manifestation of antiretroviral therapy with the development of an immune reconstitution syndrome to an underlying pathogen such as DMAC, *Mycobacterium tuberculosis* or cryptococcus.

Fever persisting for a prolonged time may be the first presenting symptom of patients with systemic infections such as PCP [13], cryptococcal disease [14], HSV [15], syphilis and infective endocarditis. Fever and personality change have been reported for cryptococcal meningitis, HSV and VZV encephalitis.

Another cause of chronic fever in HIV-seropositive individuals, not addressed elsewhere in these guidelines, is Bartonellosis, an infection caused by *Bartonella henselae* or *Bartonella quintana* [16]. It is associated with profound immunosuppression, usually with a CD4 count <50 cells/μL [17], so is less common in the post-HAART era. Individuals can present with non-specific features such as fever, lymphadenopathy, hepatosplenomegaly, abdominal pain, anaemia or elevated alkaline phosphatase [17]. More specific features include bacillary angiomatosis in which cutaneous lesions that can be friable, red, vascular and exophytic proliferative lesions, non-descript papules or subcutaneous nodules may be observed [18]. These can be difficult to distinguish from the lesions of Kaposi's sarcoma. Other presentations include osteolytic bone lesions and bacillary peliosis (usually caused by *B. henselae*) where patients can present with fever, abdominal pain, raised alkaline phosphatase and hypodense lesions on computed tomography of the liver and occasionally the spleen [18]. Rarer presentations include nodular or ulcerated lesions of the gastrointestinal tract, which can present with haemorrhage,

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respiratory tract lesions or neurological manifestations including aseptic meningitis. Neuropsychiatric presentations have been described [19]. Focal necrotising lymphadenopathy is more commonly associated with higher CD4 T-cell counts. Diagnosis involves culture and PCR of blood or biopsy specimens and serology [20]. Treatment is with erythromycin 500 mg qid orally or doxycycline 100 mg bd for at least 3 months, though other macrolides may also be effective [18].

Other, less common causes of prolonged fever include drug-induced fever and thromboembolic disease.

9.2 Clinical evaluation

9.2.1 A detailed history should include:

- Symptoms from all major systems;
- All general complaints: e.g. fever, weight loss, night sweats, headaches and rashes;
- Travel and residence history including contact with TB, illness whilst away including possible exposure to ticks and other vectors, malaria prophylaxis and pre travel vaccinations received;
- Previous illnesses including TB, surgery and psychiatric problems;
- Drug history, including over-the-counter medications, prescription medications and any illicit substances including the use of paraphernalia;
- Immunization status;
- Family history;
- Occupational history, which should include exposure to chemicals, animals;
- Sexual history, including details of any genital ulceration;
- Personality change.

9.2.2 Examination of the patient should include:

- Documentation of fever (the fever should be measured more than once and with another person present if factitious fever is suspected);
- Awareness that diseases such as brucellosis, borreliosis and Hodgkin disease tend to cause recurrent episodes of fever;
- Careful examination, particularly looking for rashes, lymph node enlargement, signs of arthritis, new/changing cardiac murmurs, hepatosplenomegaly, abdominal tenderness or rigidity, fundoscopic changes and neurological deficits;
- Mucosal examination (intraoral and genital);
- Physical examination repeated daily if the patient is in hospital (careful observation is required if patient is monitored as an outpatient as new signs and symptoms may develop).

9.2.3 Initial investigations

- CD4 cell count;
- Full blood count (FBC), urea and electrolytes (U&E), C-reactive protein (CRP), liver function test (LFT), lactate dehydrogenase (LDH);
- Cryptococcal antigen if CD4 count <200 cells/μL;
- Syphilis serology;
- Blood cultures to include mycobacterial culture;
- Culture urine, sputum (include mycobacterial culture pending CD4 cell count);
- Chest X-ray;
- Molecular virology studies (hepatitis screen, CMV);
- Arterial blood gases and at rest and ambulatory oxygen saturation;
- Echocardiography if murmur or endocarditis suspected;
- ANA, rheumatoid factor if connective tissue disease suspected.

Table 9.1 Common diagnoses following the investigation of HIV associated PUO

Infection
DMAC
Mycobacterium tuberculosis
Bacterial infections
Leishmania
Pneumocystic Jirovecii pneumonia
Histoplasmosis
CMV end organ disease
Viral (hepatitis B, C, herpes virus, adenovirus) Neoplastic/Lymphoproliferative
Lymphoma
Kaposi's sarcoma
Castleman's disease

9.3 The choice and utility of invasive diagnostic tests

Whilst the majority of diagnoses in PUO may be achieved through the use of simple microbiological tests, such as blood cultures and respiratory specimens, invasive tests may be required when such measures fail to elucidate the cause or when a diagnosis is urgently sought. (See Table 9.1 for a list of common diagnoses).

Several published studies report on the use of histopathological examination of samples acquired from bone marrow, lymph nodes, liver and lung. Fewer data exist on histopathological examination of tissue from other sites such as intestine, skin, oesophageal, brain, mediastinal nodes and lumbar puncture. Choice of further investigation is likely to be dictated by positive findings from clinical evaluation and baseline investigations (see flow diagram in Fig. 9.1).

- When tissue specimens are collected, there should always be one specimen sent to microbiology and one specimen sent to the histopathology laboratory. It is important to give complete clinical information to laboratory staff (including HIV status) to ensure appropriate tests are carried out in a timely fashion by an appropriately qualified person (level of evidence IV).

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Fig. 9.1 PUO in an HIV-seropositive patient.

It is good practice to discuss with the laboratory prior to collecting the sample which diagnoses you are considering as samples may need to be sent to another hospital for analysis.

- Investigations should be undertaken promptly as immunosuppressed patients are prone to rapid clinical deterioration. Advice from a physician experienced in HIV and opportunistic infections should be sought on choice of investigations and use of HAART (level of evidence IV).

9.3.1 Bone marrow examination (BME)

The diagnostic utility of bone marrow examinations in HIV-seropositive persons with PUO has been reviewed in a number of studies [21–23]. A diagnosis is identified in around one-third to one-half of all patients. Whilst the ultimate diagnosis was frequently obtained at other sites, BME was the only site in a minority of cases in most studies [21–24].

Diagnosis by BME may be achieved through bone marrow culture, visualization of granulomas and/or histologically apparent organisms. Special stains for mycobacteria and fungus, and immunohistostaining for lymphoma should be requested. If other diagnoses such as Castleman disease, visceral leishmaniasis and *Penicillium marneffei* are under consideration then discuss with a histopathologist and, if the patient is not under the care of an HIV or infectious disease specialist, then contact your local HIV or Infectious disease department for advice.

9.3.2 Fine needle aspirate (FNA) of lymph nodes

FNA is a worthwhile procedure in patients with adenopathy and fever. Sampling is quick and easy to perform and may obviate the need for more invasive sampling and enable immediate treatment of specific infections [25,26]. In one large reported series, which included more than 650 samples, a diagnosis was reached in 80% of cases with malignancy accounting for 13% and infection 14% (mainly mycobacterial). A definitive diagnosis was associated with deep aspirate location and lesion size >2 cm [27].

The procedure is associated with a low rate of uninterpretable slides/inadequate sample or false-negative results. In these situations consideration should be given to either lymph node sampling or surgical excision of the lymph node.

9.3.3 Lymph node sampling

Lymph node biopsy is a useful alternative to FNA. It has been shown to have a good diagnostic yield in patients with smear-negative TB [28]. If Castleman disease is suspected biopsy or excision of the lymph node may be preferable to FNA due to the focal nature of Castleman disease within lymph nodes.

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9.3.4 Percutaneous liver biopsy (PLB)

The presence of hepatomegaly or splenomegaly have been reported to be the most important factors in predicting the usefulness of the PLB, with a positive predictive value (PPV) of 86.1% and negative predictive value (NPV) of 68.2%. In patients with tuberculosis, an increased alkaline phosphatase and hepatomegaly had a PPV of 86.4% and NPV of 71.4% [29].

9.3.5 Imaging

Imaging plays a key role in the diagnostic work up in PUO. It assists in identification of focal pathology that may be amenable to biopsy in order to get a tissue diagnosis.

A chest X-ray film should be part of the routine investigations. More detailed investigations should be based on clinical symptoms and signs and may include CT/MRI of chest, abdomen and pelvis. There is emerging evidence that 18-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scanning can help identify the source of disease when earlier investigations have been unsuccessful [30,31].

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10 Travel-related opportunistic infections

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10.1 Methods

The PubMed database was searched under the following headings: HIV or AIDS and malaria, *Malaria falciparum*, leishmaniasis or *Leishmania* spp, *Trypanosoma cruzi*, American trypanosomiasis or Chagas disease, histoplasmosis, *Histoplasma capsulatum*, blastomycosis, *Blastomyces dermatitidis*, coccidioidomycosis, *Coccidioides immitis*, penicilliosis or *Penicillium marneffei*.

10.2 Introduction

According to figures from the Health Protection Agency, travel abroad by United Kingdom (UK) residents followed the international trend and continued to increase with an estimated 66.4 million visits overseas in 2005. More males than females travelled from the UK and were, on average, between 35 and 44 years of age. Around two-thirds of UK residents travelled for holidays in 2005, the majority to other countries in the European Union (EU). Since 2003, visits to tropical destinations have increased by 28% compared to a decrease of 0.2% for visits within the EU. The number of visits made to see friends and relatives continued to increase at a higher rate (23% since 2003). These figures are particularly relevant to travellers with HIV either involving those with the disposable income to travel or those visiting family overseas. People living with HIV are affected by the usual coughs and travel-associated diarrhoea, however, and this may interfere with their adherence to antiretroviral medication and so pose a greater problem. Anecdotally, patients may discontinue ART while travelling, bringing risks of seroconversion-like illness to others and opportunistic infections.

10.3 Malaria

10.3.1 Background and epidemiology

Malaria is a protozoal infection transmitted in endemic areas by the bite of a female anopheles mosquito. There are five main species of parasite that can infect humans but *Plasmodium falciparum* is the most serious and can be rapidly fatal. Every year, 1500–2000 cases are reported to the Health Protection Agency (HPA) Malaria Reference Laboratory (MRL), and there are nine to 13 deaths in the UK [1]. Most of these are related to delay in diagnosis.

In the UK the burden of falciparum malaria falls heavily on those of African and south Asian ethnicity. According to the Health Protection Agency the commonest reason for presenting with malaria in the UK is 'visiting family from country of origin' and migrants now living in the UK are often poorly compliant with malaria precautions, believing themselves not to be at risk of malaria [2]. However, immunity to malaria wanes quickly and this group of patients should be targeted for advice regarding avoiding mosquito bites and taking prophylactic antimalarials [1]. Evidence from South Africa suggests that people with HIV who are non-immune to malaria are at higher risk of severe disease or death from malaria [3,4].

10.3.2 Presentation

Observational and prospective studies from Africa suggest that the likelihood of severe malaria and death is increased with HIV coinfection in areas of unstable malaria transmission [4]. The increased incidence of severe malaria is chiefly seen in individuals with CD4 T-cell counts $<200/\mu L$ [3], but among individuals with no immunity to malaria there does not appear to be an increased incidence of parasitaemia *per se* [5]. In settings of year-round malaria transmission where most adults are semi-immune to malaria, the incidence of parasitaemia and clinical malaria are increased in individuals with HIV infection [5].

Malaria presents non-specifically with fever, headache, arthralgia, myalgia, diarrhoea and sometimes features of bacterial infection. Patients may be severely unwell and hypotensive, requiring intensive care unit (ICU) involvement early in the hospital admission. Other than severity there is no evidence that HIV serostatus modifies presentation. Complications of malaria include hyperparasitaemia, acute renal failure, hypoglycaemia, disseminated intravascular coagulopathy, lactic acidosis, fulminant hepatic failure and cerebral malaria [6]. Mortality is still around 20% with higher rates in HIV-seropositive individuals when treated in Africa. Controversy remains concerning the impact of malaria on mother-to-child transmission of HIV but HIV-seropositive women with malaria have an increased incidence of anaemia, infants with low birth

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weight, prematurity and infant mortality due to malarial parasites preferentially binding to the placenta [7].

10.3.3 Diagnosis

- Malaria should be diagnosed in the same way as in HIV-seronegative individuals, using a combination of thick and thin blood films with or without a rapid diagnostic (antigen) test in HIV-seropositive individuals (category IV recommendation).

In practice, this involves considering the diagnosis in anyone with fever who has returned from an endemic area. Falciparum malaria usually presents within 3 months of their return but non-falciparum malaria may recrudesce many years after their return. There is little information on how HIV may modify this but partial immunity may delay the presentation of falciparum malaria.

Malaria should be suspected in anyone returning from an endemic area, as the presentation, especially in the semi-immune person, is very variable. Diagnosis is made by a thick and thin blood film although highly sensitive and specific diagnostic dipsticks now exist [8–10]. Thick films (to diagnose malaria and estimate the percentage parasitaemia) and thin films (for speciation) should be collected on all patients (category IV recommendation) [6]. Rapid diagnostic tests for malaria antigens may be helpful if malaria is suspected but blood films are negative. In HIV-seronegative individuals they are less sensitive but are useful for laboratories with less experience in interpreting malaria blood films [6]. There is limited information on their performance in HIV-seropositive individuals. Current guidelines recommend that any patient considered to be at risk of viral haemorrhagic fever should have a malaria film done under category 3 conditions first [11].

10.3.4 Treatment

- Follow the World Health Organization guidelines [12]. Antiretroviral drug interactions are hypothetical except for that between efavirenz and amodiaquine, a combination which should be avoided.
- Non-severe falciparum malaria should be treated with oral artemether–lumefantrine or oral quinine followed by doxycycline, or with Malarone (atovaquone–proguanil) (category IV recommendation).
- Severe falciparum malaria ($>2\%$ parasitaemia $\pm$ organ dysfunction) should be treated initially with intravenous artesunate where available or with quinine by intravenous infusion with cardiac monitoring when artesunate cannot be administered. Individuals with severe malaria should be referred promptly to a specialist unit (category IV recommendation).

The many potential antimalarial and antiretroviral drug interactions are summarized below (Table 10.1) [13]. However, most do not seem to be clinically problematic despite many drugs being metabolized via the same hepatic cytochrome pathway. The interactions are therefore largely hypothetical except for efavirenz and amodiaquine, which should not be co-administered. The choice of antimalarials is therefore determined by the species and severity of the malaria with similar considerations as for HIV-seronegative individuals [6].

Uncomplicated falciparum malaria should be treated with oral artemether–lumefantrine (Co-artem, Riamet). If the weight is >35 kg the treatment schedule is four tablets at 0, 8, 24, 36, 48 and 60 h. Alternatives are oral quinine (600 mg tid po for 7 days plus doxycycline 200 mg orally once a day for 5–7 days) or Malarone (atovaquone–proguanil) (four tablets daily orally for 3 days) if there are no complications.

There is a potential interaction between ritonavir and quinine, which may result in increased quinine levels [14]. If individuals meet criteria for parenteral quinine, they should still receive a standard loading dose of quinine (see below) but protease inhibitors should be stopped until the patient is stable and able to take oral medications. There should also be increased vigilance for signs of quinine toxicity, including evidence of prolongation of the QT interval, and quinine dose reduction may be required if any signs of toxicity are noted. Non-nucleoside reverse transcriptase inhibitors (NNRTI) may decrease quinine levels and since quinine metabolism may be enhanced with malaria this may result in significant underdosing with standard doses of quinine [15,16]. NNRTI and quinine should ideally be avoided but if the patient is already on NNRTI and quinine must be prescribed, the dose of quinine may need to be titrated against the clinical response and the patient monitored carefully for signs of toxicity, such as abnormalities on cardiac monitoring. Concerns have been raised about the safety and efficacy of artemisinin-based combination treatments when combined with antiretroviral therapy [13]. Artesunate plus amodiaquine combinations have reduced efficacy, as compared to artemether plus lumefantrine (co-artemether), and when combined with efavirenz have been associated with hepatotoxicity and neutropenia [17–19]. Preliminary data also suggest that lumefantrine exposure is increased with nevirapine (contrary to what would be expected with an enzyme inducer). The mechanism is unknown, but it should be noted that lumefantrine exposure in controls was variable, and in many cases, low. At present there are insufficient data to recommend dose modification but increased vigilance is advised [20].

It was previously suggested that co-artemether (Riamet) should be avoided in patients taking protease inhibitors due

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Table 10.1 Potential antimalarial and antiretroviral drug interactions

Drug name	Interaction with antiretroviral	Action required
Chloroquine	Ritonavir can potentially increase chloroquine levels through enzyme inhibition although no formal studies	Monitor for signs of chloroquine toxicity especially cardiotoxicity (QT interval prolongation)
Mefloquine	NNRTIs can potentially decrease mefloquine levels through enzyme induction	Caution Monitor for reduced signs of clinical effectiveness
	PIs can potentially inhibit metabolism of mefloquine through cytochrome P450 3A4. Ritonavir inhibits p-glycoprotein, which may also increase mefloquine levels.	Caution Monitor for signs of mefloquine toxicity such as neuropsychiatric events or changes in cardiac rhythm
Quinine	NNRTIs can decrease levels of quinine via induction of CYP3A4	Caution Monitor for reduced clinical effectiveness. Check quinine levels if possible. May need to increase quinine dose
	PIs can increase quinine levels through inhibition of CYP3A4	Caution Monitor for signs of toxicity. Cardiac monitoring recommended for signs of prolonged QT interval. Check quinine levels if possible and dose reduce.
Artemether/lumefantrine (Riamet)	NNRTIs can increase or decrease levels of lumefantrine and artemether	Caution Monitor for signs of reduced clinical effect or increased toxicity. Lumefantrine may cause cardiotoxicity
	PIs can potentially increase lumefantrine levels due to inhibition of CYP3A4 PIs can potentially decrease artemether's conversion to its active form	Extreme caution Monitor for signs of cardiotoxicity. Refer to manufacturer's literature
Atovaquone/proguanil (Malarone)	PIs may reduce levels of both components	Currently no recommendation for dose modification but clinicians advised to watch for prophylaxis failures
	Efavirenz reduces levels of both components	Increased vigilance for prophylaxis failures.

Antiretroviral drugs, especially the NNRTIs and boosted PIs, have several important drug–drug interactions. This table lists some examples of drug–drug interactions with antiretrovirals and agents used in the treatment and prophylaxis of malaria. As data and advice change frequently, this information should always be interpreted in conjunction with the manufacturer's information (www.medicines.org.uk). Other useful web-based reference sources include the Liverpool HIV drug information website (www.hiv-druginteractions.org) and the Toronto Clinic (www.hivclinic.ca/main/drugs_interact.html).

to drug interactions. More recent pharmacokinetic data has suggested that when healthy volunteers received lopinavir/ritonavir with co-artemether, the area under the curve (AUC) and C_{max} of artemether was only modestly reduced and that conversely lumefantrine AUC was increased, without consequences to lopinavir levels [21]. While this may suggest co-artemether may be given with select antiretrovirals and they may be considered as preferred agents in the treatment of uncomplicated malaria further information on the efficacy and toxicity of these combinations in HIV-seropositive individuals is required and it must be emphasized that there is still limited experience of the use of these agents in HIV-seropositive individuals in Western settings.

Severe or complicated falciparum malaria is defined as cases with shock, renal impairment, acidosis, pulmonary oedema or acute respiratory distress syndrome, impaired consciousness or seizures, hypoglycaemia, very low haemoglobin (defined by WHO as <5g/dL [12]), haemoglobinuria or disseminated intravascular coagulopathy [6]. It should be treated with a parenteral regimen, which should also be used in cases where the parasitaemia level is $>2\%$, or when the individual is unable to take oral medicines. Under these circumstances falciparum malaria is treated with intravenous artesunate 2.4 mg/kg daily, given at 0, 12, 24 h then daily to complete a 7-day course combined with doxycycline 200 mg once a day. Intravenous quinine (loading dose: 20 mg/kg intravenously infused over 4 h, maximum dose 1.4 g, then 10 mg/kg intravenously by infusion over 4 h every 8 h for 48 h, then bid thereafter, until the individual is able to take oral medication) is an alternative. Rapid referral should be made to a specialist centre (category IV recommendation). The loading dose of quinine should be withheld if quinine or mefloquine has been administered in the previous 12 h. Quinine prolongs the QRS and QT intervals and can induce hypoglycaemia, so treatment must be given while connected to a cardiac monitor with regular measurement of blood glucose levels. There is a potential for increased cardiac problems due to an interaction between quinine and ritonavir.

The treatment of choice for non-falciparum malaria (*P. ovale*, *P. vivax*, *P. malariae*) is a 3-day course of oral chloroquine (600 mg orally, then 300 mg after 6–8 h then 300 mg daily for 2 days) followed by 14 days of primaquine (*P. vivax:* 30 mg orally once a day; *P. ovale:* 15 mg once a day) to eradicate the liver stages. Primaquine is not required for *P. malariae* [6]. Patients should be tested for G6PD deficiency before starting primaquine to quantify and minimize the risk of haemolysis. Patients with G6PD deficiency can be managed with lower-dose primaquine for longer, but specialist advice should be sought.

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10.3.5 Prophylaxis

- All HIV-seropositive individuals who travel to malaria-endemic areas should be offered malaria prophylaxis and given general advice on how to avoid mosquito bites as part of a comprehensive pre-travel assessment (category IV recommendation).

HIV-seropositive travellers are at higher risk of severe malaria, and prevention of malaria should be strongly promoted. They should receive the same general travel advice concerning the prevention of malaria as the HIV-seronegative traveller, i.e. the ABCD of malaria prevention should be emphasized: Awareness of risk, Bite prevention, Chemoprophylaxis and prompt Diagnosis and treatment (*see* [22]).

The advice regarding chemoprophylaxis depends on the area visited, time spent and medical history and specialist advice is available from the National Travel Health Network and Centre (NaTHNaC) [23] funded by the Department of Health for England or 'Fit for Travel' [24] in Scotland.

Although co-trimoxazole may reduce the risk of developing malaria, HIV-seropositive patients receiving co-trimoxazole should still receive standard malaria chemoprophylaxis and follow all the general advice around prevention of malaria.

The main options for chemoprophylaxis are mefloquine 250 mg orally once weekly, Malarone (atovaquone–proguanil) one tablet once daily and doxycycline 100 mg orally once daily. Chloroquine-based regimens (chloroquine 300 mg once weekly with proguanil 200 mg orally once daily) are less used now due to widespread resistance. Regimens are started 1 week prior to travel and continued for 4 weeks after return with the exception of Malarone (atovaquone–proguanil) which is started 1–2 days before travel and continued for 1 week after return and mefloquine which should be started 3–4 weeks prior to travel, if treatment naïve, to give the individual time to develop neurocognitive side effects and to change to an alternative agent, if necessary, prior to travel.

- Mefloquine is contraindicated in patients with a history of epilepsy, neuropsychiatric disorders including depression, liver impairment and cardiac conduction disorders. Neurocognitive side effects with mefloquine are more common in women, those with low body mass index (BMI), those embarking on long-term travel and those with a history of recreational drug use [25,26]. They are particularly common in younger adults and many authorities would therefore avoid this agent in younger adults, particularly if female, with a low BMI or with a history of recreational drug use. In pregnancy, the use of mefloquine requires careful risk–benefit analysis and specialist advice should be sought. Mefloquine antagonizes the anticonvulsant effect of valproate and increases the incidence of cardiac conduction problems with moxifloxacin.
- Malarone is safe and well tolerated. Efavirenz and protease inhibitors may reduce both atovaquone and proguanil levels and, although there are currently no recommendations to adjust the dose of Malarone, clinicians and their patients must remain vigilant for prophylaxis failures [27].
- Doxycycline should be avoided in hepatic impairment, in those who cannot ensure regular administration of a sun block to prevent photosensitisation, and also in pregnant women and children under the age of 12 years.

Other areas of advice to emphasize include the use of high percentage (greater than 20%) diethyltoluamide (DEET), covering up extremities when out after dark and use of permethrin-impregnated mosquito nets to sleep under.

10.4 Leishmaniasis

10.4.1 Background and epidemiology

Leishmaniasis is a group of diseases caused by protozoa of the genus *Leishmania* that are transmitted by sandflies, and, rarely, by injecting drug use. In the UK, most imported cases of visceral leishmaniasis come from the Mediterranean, East Africa or India, and cutaneous leishmaniasis from Central America or the Middle East [28]. Visceral leishmaniasis in HIV-seropositive individuals usually occurs in those with CD4 counts below 200 cells/μL [29].

10.4.2 Presentation

Leishmania cause three types of disease:

- Visceral (kala azar), which usually presents with systemic features of fever and weight loss along with hepatosplenomegaly (with splenic enlargement most prominent), with or without bone marrow involvement;
- Mucocutaneous, with destructive lesions of the mucous membranes of the nose or mouth;
- Cutaneous, causing skin ulcers, usually on the limbs or face.

Most reported cases of HIV/*Leishmania* co-infection in Europe are of visceral leishmaniasis [30]. Cases may be associated with a history of intravenous drug use [31]. Visceral leishmaniasis usually, but not always, presents in the same way as it does in HIV-seronegative people; the systemic features may be mistaken for other opportunistic infections.

Cutaneous leishmaniasis may present as it does in immunocompetent individuals with a papule that progresses to a chronic ulcer, but a wide range of atypical skin lesions may occur, and may be mistaken for Kaposi's

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sarcoma or bacillary angiomatosis. Isolated mucocutaneous leishmaniasis in association with HIV infection appears to be very rare in Europe, probably as *L. infantum*, which causes most visceral leishmaniasis in Europe, rarely causes mucosal lesions. However, any patient with a suspected leishmanial lesion on the face should be seen urgently by a specialist. Mucocutaneous leishmaniasis may be seen in cases acquired in Central or South America where the infecting species have greater tropism for mucous membranes.

10.4.3 Diagnosis

- Diagnosis of leishmaniasis requires parasitological or histological confirmation (category III recommendation).
- Where leishmania is strongly suspected but standard tests are negative, discussion with a tropical medicine specialist is recommended to advise on the utility and interpretation of newer tests in the setting of HIV infection (category IV recommendation)

Diagnosis depends on parasitological or histological demonstration of *Leishmania*. Parasitological diagnosis is most useful because identification of *Leishmania* species may guide appropriate treatment. In the context of HIV, standard diagnostic tests may be less sensitive and expert advice should be sought (category IV).

10.4.3.1 Visceral leishmaniasis. Parasitological diagnosis may be made by microscopy, culture or PCR. Appropriate specimens include [30,32,33]:

- Splenic aspirate: this has the highest sensitivity, but should only be performed by a practitioner trained in the technique;
- Bone marrow aspirate;
- Biopsy specimens (such as lymph node or skin).

It is strongly recommended to liaise with the local tropical disease and parasitology service before taking specimens. Some transport media (e.g. those with antifungal agents) may inhibit leishmania culture so specimen transport should be discussed with the laboratory.

Histological diagnosis may be made on biopsy of bone marrow, lymph node, liver, skin or other tissue.

Serological tests include the direct agglutination test and ELISA to detect antibodies to recombinant K39 antigen (rK39). The sensitivity of both may be reduced in HIV/*Leishmania* coinfection [32] due to low levels of antibody in HIV-seropositive individuals [34].

10.4.3.2 Cutaneous leishmaniasis. Parasitological or histological diagnosis (preferably both) may be made from a skin biopsy [32]. As above, it is important to discuss the matter with a parasitology laboratory to ensure that specimens are handled appropriately.

Serological tests are not helpful in the diagnosis of cutaneous leishmaniasis.

10.4.4 Treatment

- Therapy for leishmaniasis should be co-ordinated with the local tropical medicine service (category IV recommendation).
- Liposomal amphotericin B is the treatment of choice for visceral leishmaniasis (category III recommendation).
- Secondary prophylaxis of visceral leishmaniasis is with liposomal amphotericin B or intravenous pentamidine (category III recommendation).

10.4.4.1 Visceral leishmaniasis. The treatment of choice for visceral leishmaniasis in an HIV-seropositive person is liposomal amphotericin B 4 mg/kg for 10 doses given on days 1–5, 10, 17, 24, 31 and 38 [35]. Although liposomal amphotericin B is the lipid formulation available in the UK in some European countries alternative lipid formulations may be used; amphotericin B lipid complex has also been used for treatment of visceral leishmaniasis [36]. Review of clinical studies has suggested that treatment with liposomal amphotericin B is as efficacious but less toxic than treatment with pentavalent antimonials [37]. HIV-seropositive individuals have a high relapse rate after treatment for leishmaniasis [36]. Secondary prophylaxis of visceral leishmaniasis is the standard of care in Europe because in the pre-ART era, relapse after treatment was almost inevitable [37,39]. Pentamidine (4mg/kg every 2 weeks intravenously) [40] or liposomal amphotericin B (5 mg/kg every 3 weeks intravenously) may be used, while amphotericin B lipid complex has also been used for secondary prophylaxis of visceral leishmaniasis [41,42]. There is insufficient evidence to support the use of one specific regimen over another and this is best discussed with the local tropical disease service. Case series describe the use of oral miltefosine treatment when standard treatment fails [43,44]. Case reports, however, describe the failure of this approach when miltefosine is used alone [45]. The use of pentavalent antimonials in combination with or followed by oral miltefosine, may be a better option when standard treatment fails but more data are needed before firm recommendations can be made [46,47]. Complex cases should be discussed with the local tropical medicine service.

10.4.4.2 Cutaneous leishmaniasis. Cutaneous leishmaniasis can be treated with local infiltration of sodium stibogluconate or systemic treatment, depending on the species [48], although there is limited experience of local therapy in individuals with HIV infection. This is best discussed with the local tropical disease service.

10.4.5 Prophylaxis

Primary prophylaxis of leishmaniasis is not recommended.

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10.4.6 Impact of HAART

For patients not taking HAART at the time of diagnosis, there is no specific evidence to guide when HAART should be started but expert opinion suggests this should be as soon as the patient is stable on antileishmanial therapy. There are few data to guide whether and when to stop secondary prophylaxis of visceral leishmaniasis. Some authors recommend that secondary prophylaxis can be stopped if leishmaniasis has been treated successfully, the patient is stable on HAART and the CD4 T-cell count has been above 200–350 cells/μL for 3–6 months [36,49]. However, relapse is described even among patients with successful treatment and CD4 T-cell counts >200 cells/μL [50]. Cases of leishmaniasis IRIS are described with new or worsening skin lesions including ulcers, mucocutaneous ulcers in the mouth or penis, post-kala-azar dermal leishmaniasis or uveitis [51,52]. There are also reports of visceral leishmaniasis presenting as an immune reconstitution phenomenon after the start of antiretroviral therapy [53].

There are multiple overlapping toxicities with HIV medication and treatment for leishmaniasis and liaison with an HIV pharmacist is recommended.

10.5 Chagas disease (*Trypanosoma cruzi*)

10.5.1 Background and epidemiology

Chagas disease or American trypanosomiasis is caused by a parasite, which is a member of the genus *Trypanosoma*; *Trypanosoma cruzi*. It is confined to Central and South America and its distribution extends from Mexico in the north to the northern half of Argentina and Chile in the south. *T. cruzi* is spread by bloodsucking triatomine insects, also known as kissing bugs, found in particular in rural areas [54]. There is increasing recognition that reactivation of *Trypanosoma cruzi* infection can cause disease in patients with advanced immunosuppression, including HIV-seropositive individuals who have lived or travelled to endemic areas.

10.5.2 Presentation

T. cruzi causes two main types of disease in people with HIV:

- Neurological disease; space-occupying lesions or meningoencephalitis
- Myocarditis

Clinical syndromes are most common in individuals with CD4 T-cell counts <200 cells/μL [55]. Neurological syndromes are the commonest presentation, comprising 75% of presentations of Chagas disease in untreated HIV-seropositive patients. Patients can present with features of a space-occupying lesion, encephalitis, or meningoencephalitis [56]. Clinical symptoms are typically of fever, headaches, seizures, vomiting and focal neurological signs and mimic toxoplasma encephalitis [54]. Myocarditis is the second most common presentation seen in approximately a third of cases, often with concomitant neurological disease. Myocarditis is often asymptomatic and only detected at autopsy but can present with arrhythmias or heart failure [54,57]. Chagas disease may also affect the digestive tract and cause megaoesophagus or megacolon. Chagas disease should be suspected in patients from the endemic areas of Central and South America or with a history of blood transfusions or intravenous drug use with contacts from these areas.

10.5.3 Diagnosis

- Diagnosis of Chagas disease requires a combination of imaging, serology, PCR and if available histological confirmation (category III recommendation).
- Asymptomatic individuals with HIV infection from an endemic area should be screened with serology and, if positive, be further evaluated for disease (category IV recommendation)

For neurological disease, imaging studies characteristically report space-occupying lesions similar to those described for toxoplasma encephalitis [58]. CSF examination typically describes lymphocytic pleocytosis and elevated protein with possibly low glucose [54]. Serological tests are generally not diagnostic for reactivation, indicating only previous exposure. PCR testing helps separate past exposure from reactivation [59]. Parasitological studies, including thick smears or Strout's concentration method, and CSF smears (ideally after centrifugation) are usually necessary [60]. Biopsy specimens may also aid in the diagnosis if other tests are equivocal. As there is often misdiagnosis, failure to respond to initial treatment for toxoplasmosis should raise suspicion in high-risk patients.

Currently, it is recommended that all HIV-seropositive people with epidemiological risk factors for Chagas disease be tested for antibodies to *T cruzi* to detect latent infection and, if positive, should be further evaluated, in discussion with a specialist tropical disease centre, for neurological, intestinal and cardiological disease.

10.5.4 Treatment

- Therapy for Chagas disease should be co-ordinated with the local tropical medicine service (category IV recommendation).
- Benznidazole is the treatment of choice for acute primary infection or reactivation of Chagas disease, with nifurtimox the alternative (category III recommendation).
- Treatment should be considered for asymptomatic individuals with HIV infection and positive serology (category III recommendation)

The recommended treatment for *acute primary infection or reactivation Chagas disease* in HIV-seropositive patients is

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benznidazole 5 mg/kg daily divided in two doses for 60–90 days. A higher dose may be needed in acute meningo-encephalitis. Nifurtimox 8–10 mg/kg daily divided in three doses for 60–120 days is considered an alternative. Following treatment, secondary prophylaxis with benznidazole 5 mg/kg three times weekly is recommended: there is no evidence to guide the optimum duration, but the duration is likely to be governed by the same factors as other opportunistic infections and be influenced by the immunological and virological response to HAART. These drugs have important side-effects and treatment should be supervised by a specialist tropical disease centre.

For *asymptomatic individuals seropositive for* T. cruzi, *or individuals with chronic disease*, a course of treatment with benznidazole or nifurtimox (regimens as above) should be considered. For individuals with virological suppression and immunological responses to HAART, the risks and benefits of treatment should be considered on a case by case basis [61,62]. Individuals not taking, and unable to or unwilling to start, HAART should be offered treatment with benznidazole or nifurtimox.

Following treatment, secondary prophylaxis is not usually required for asymptomatic individuals seropositive for *T. cruzi* if on HAART, but if the individual is not able to take HAART, options are either to consider secondary prophylaxis, if the benefits outweigh the risks, or alternatively to monitor the patient closely off further treatment.

10.5.5 Prophylaxis

There is no role for primary prophylaxis.

10.5.6 Impact of HAART

The prognosis is now generally considered to be good [63]. Since clinical cases and reactivation are related to CD4 T-cell count, it is logical that HAART will decrease the incidence of reactivation and, anecdotally, receipt of HAART has been associated with a slower tempo of disease progression in those with disease [59].

10.6 Histoplasmosis, blastomycosis and coccidioidomycosis

10.6.1 Background and epidemiology

Dimorphic fungi of medical importance in HIV-seropositive individuals are *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis* and *Penicillium marneffei*. Each of these is geographically restricted. The route of infection is via inhalation of microconidia (or arthroconidia for *C. immitis*) that are aerosolized and can be dispersed many miles by air. Immunocompetent hosts develop localized pulmonary disease, which is frequently asymptomatic while those with chronic lung disease develop chronic pulmonary syndromes and individuals with immunosuppression develop disseminated disease. In the post-HAART era each of these presentations can be encountered in HIV-seropositive individuals.

H. capsulatum var *capsulatum* is found in mid-western and south-eastern states of the United States, the Caribbean, Central America, South America, Africa, and in pockets elsewhere throughout the world [64]. *H. capsulatum* var *duboisii* is found mainly in West and Central Africa [65]; it causes mainly extra-pulmonary disease. *B. dermatitidis* is found in the centre of the United States, along the St Lawrence Seaway and around the Great Lakes of the United States and Canada [66]. *C. immitis* is found in the south-western part of the United States and in northern Mexico [67].

An infection should be suspected in someone who has resided in an endemic area, although for some dimorphic fungi short-term exposure during travel to an endemic area is sufficient. Infections can represent either reactivation or primary infection.

10.6.2 Presentation

Individuals with well preserved CD4 cell counts present similarly to HIV-seronegative individuals. Infection may be asymptomatic [68]. Clinical features, if present, involve cough and fever with focal consolidation and hilar lymphadenopathy on chest radiography [69]. Coccidioidomycosis can present with either asymptomatic infection or as a pneumonic illness [67].

Pre-HAART, the most frequent manifestation of dimorphic fungal infection was as acute disseminated infections. General features of disseminated histoplasmosis include fever, weight loss and rash [70] and disseminated blastomycosis may be associated with neurological disease [66]. Physical signs include focal consolidation or bilateral crackles, lymphadenopathy, hepatosplenomegaly, rash and frequently hypotension. In many cases of disseminated disease respiratory signs and symptoms are minimal.

Chest radiographs for histoplasmosis reveal interstitial, nodular or miliary infiltrates although occasionally demonstrate more focal disease. Focal pulmonary disease may be less common with coccidioidomycosis [71]. Cavitary disease is rare but has been reported for histoplasmosis and coccidioidomycosis [72]. A variety of extra-pulmonary manifestations are associated with disseminated disease. Histoplasmosis may be associated with oropharyngeal and gastrointestinal ulceration. Patients may present with a sepsis syndrome and hypotension [70]. Rarer manifestations include meningitis, endocarditis or involvement of the adrenal gland [73]. CNS disease may also occur with *B. dermatitidis* infection with up to 40% of individuals with AIDS having CNS disease in one pre-HAART series [66]. Noteworthy features of coccidioidomycosis include eosinophilia, meningitis and a syndrome of weight loss and

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fever without focal disease. Although in the pre-HAART era coccidioidomycosis most often presented as disseminated or extensive pulmonary disease, and rarely presented as an asymptomatic infection, in the post-HAART era there has been increasing recognition of cases that are asymptomatic, which are detected with just a positive serological test or by an incidental nodule or cavity on chest radiograph [74]. These cases are associated with an undetectable HIV-1 viral load on HAART and with a mean CD4 T-cell count of >350 cells/μL.

10.6.3 Diagnosis

- In disseminated disease cultures of bone marrow are frequently positive (category III recommendation).
- Bone marrow trephine and culture should be performed if disseminated disease is suspected (category III recommendation).
- Diagnosis should be sought via culture and histological methods (category III recommendation).
- Consideration should be given to testing serum histoplasma antigen to follow the response to therapy in disseminated disease (category III recommendation).

Definitive diagnosis involves culture of the organism from sputum, broncho-alveolar lavage (BAL) or a biopsy specimen – which can take up to 4 weeks for growth – or identification of the yeast on a biopsy specimen or body fluid [66,67,70]. Each yeast has a characteristic appearance on biopsy. In disseminated disease, cultures of bone marrow are frequently positive and blood cultures may also be diagnostic [70]. A polysaccharide antigen test for *H. capsulatum* var *capsulatum* is available and is particularly useful in patients with disseminated disease [69] or in BAL specimens with pulmonary disease [75] but its availability is largely limited to a US reference laboratory.

Serology is positive in approximately 70% of cases with coccidioidomycosis [71].

Patients with disseminated histoplasmosis may have very high LDH levels (>600 IU/L) [76]. Diagnosis of CNS disease may be difficult as fungal stains, culture and even serological tests may all be negative. Real-time PCR assays seem to be very useful (up to 100% pick-up rate) [77], but are not yet widely available.

10.6.4 Treatment

- Localized disease should be treated initially as for HIV-seronegative individuals with itraconazole solution for histoplasmosis/blastomycosis and fluconazole for coccidioidomycosis (category IV recommendation).
- Moderately severe disseminated infection should receive induction treatment with liposomal amphotericin B 3 mg/kg/day intravenously (category Ib recommendation for histoplasmosis, category IV recommendation for blastomycosis/coccidioidomycosis).
- After induction therapy maintenance therapy should be with itraconazole or, in the case of coccidioidomycosis, fluconazole (category III recommendation).
- Itraconazole treatment should be with the oral solution and therapeutic monitoring should be performed to ensure adequate levels (category III recommendation).

For localized histoplasmosis or blastomycosis treatment is with itraconazole 200 mg bd, administered as the oral solution due to better bioavailability, and with therapeutic monitoring to check levels due to variability between individuals [78]. This recommendation represents an extrapolation of data and guidelines intended for HIV-seronegative individuals but seems appropriate for the less immunocompromised individuals who present with this form of disease (category IV recommendation). For *C. immitis* fluconazole 400–800 mg od is the preferred azole (category IV recommendation) [67]. Itraconazole 200 mg bd po (with a loading dose of 200 mg tid/300 mg bd for 3 days) can also be used for initial treatment of mild disseminated histoplasmosis in HIV-seropositive individuals [79]. Important interactions occur between itraconazole (and other azoles) and HAART (Table 7.1 in *7. Candidiasis*). Many antiretroviral drugs, including ritonavir (and other PIs), can increase levels of itraconazole (and other azoles) while azoles modify the metabolism of antiretrovirals. If concomitant HAART is required it is advisable to select agents that have minimal drug interactions and to use therapeutic drug monitoring to check both itraconazole and potentially antiretroviral agents. Specialist advice, including that from a pharmacologist with experience of these interactions, is required to effectively manage these cases.

For moderately severe disseminated histoplasmosis [70], or for disseminated blastomycosis [66] or for disseminated coccidioidomycosis [80], amphotericin B is usually used for induction treatment for the first 2 weeks of therapy. Liposomal amphotericin B at 3 mg/kg iv for 2 weeks is the preferred induction agent for moderately severe disseminated histoplasmosis in HIV-seropositive individuals, on the basis of a randomized clinical trial which demonstrated less infusion-related toxicity and nephrotoxicity and greater clinical success, as compared to conventional amphotericin B (category Ib recommendation) [81]. Although fewer data exist for other disseminated infections with dimorphic fungi, it is reasonable to consider liposomal amphotericin B at 3 mg/kg/day for 2 weeks followed by itraconazole (or fluconazole for coccidioidomycosis) for other dimorphic fungi (category IV recommendation). There is no evidence that higher doses of amphotericin

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offer any treatment advantage. Patients unable to tolerate amphotericin may be treated with intravenous itraconazole (fluconazole for coccidioidomycosis) although azoles have been little studied in moderately severe disseminated disease (category IV recommendation). After initial induction therapy for 2 weeks, maintenance therapy for the next 10 weeks should be with itraconazole oral solution 200 mg bd po with therapeutic drug monitoring as above. After this period the maintenance dose should be 200 mg od/bd with the goal of keeping the itraconazole level >4 mg/L (category III recommendation) [79]. For CNS disease with histoplasmosis up to 5 mg/kg/day liposomal amphotericin B for 4–6 weeks followed by fluconazole 800 mg od (due to better CNS penetration than itraconazole) for at least 1 year is recommended [69].

For coccidioidomycosis there are fewer clinical data but moderately severe disease is treated with liposomal amphotericin B 3 mg/kg/day intravenously followed by maintenance with fluconazole 400–800 mg od orally (category IV recommendation). Some experts recommend using fluconazole with amphotericin B in the induction phase [67] and fluconazole 800 mg od orally should be used in induction therapy, with or without intrathecal amphotericin B, when there is CNS disease [82]. Fluconazole levels do not need to be monitored.

Case reports and case series exist of the use of voriconazole and posaconazole against dimorphic fungi such as histoplasmosis and coccidioidomycosis in settings where individuals were not responding to conventional therapy, and these agents have *in vitro* activity against dimorphic fungi [83]. These agents may be considered in cases intolerant to, or failing, amphotericin B and itraconazole (category III recommendation) [67,84]. CNS coccidioidomycosis requires life-long therapy [67]. Severe pulmonary disease or granulomatous mediastinitis with histoplasmosis airway obstruction may be treated with prednisolone 60 mg histoplasmosis causing od for the first couple of weeks [69,85].

10.6.5 Prophylaxis

- Routine primary prophylaxis for histoplasmosis and related dimorphic fungi is not indicated (category IV recommendation).
- Secondary prophylaxis can be discontinued if after 1 year of antifungal therapy there has been administration of HAART for >6 months and the CD4 count is >150 cells/μL (category III recommendation).

Prophylaxis is not routinely warranted. Prophylaxis for individuals with CD4 counts <150 cells/μL who reside in an *H. capsulatum* var *capsulatum* endemic area may be considered in select cases with itraconazole 200 mg od po, which has been shown to reduce the incidence of histoplasmosis and cryptococcosis [68]. ACTG study A5038 prospectively evaluated discontinuation of maintenance therapy for disseminated histoplasmosis when antifungal therapy had been administered for at least 12 months, HAART had been administered for at least 6 months, fungal blood cultures were negative, histoplasma urinary and serum antigen results were below the limit of detection and the CD4 count was >150 cells/μL [86]. With 2 years of follow-up no relapses were noted. It is assumed that secondary prophylaxis can be stopped for other dimorphic fungi under similar conditions to those studied above.

10.6.6 Impact of HAART

The best time to initiate HAART is unknown; however, improved responses of histoplasmosis are seen with HAART, and histoplasmosis-associated IRIS tends not to be life threatening [87,88] so commencing treatment within 2 weeks of therapy seems appropriate (category IV recommendation).

Histoplasmosis has been associated with IRIS in individuals commencing HAART [89]. Manifestations include lymphadenitis, hepatitis, arthritis and uveitis. There is less information with blastomycosis and coccidioidomycosis although theoretically IRIS could occur.

10.7 Penicilliosis

10.7.1 Background and epidemiology

Disseminated *P. marneffei* infection is a common opportunistic fungal infection in patients with advanced HIV infection who live in southeast Asia and southern China [90]. It was originally isolated from bamboo rats and seems to be acquired by airborne contact with soil rather than the animals themselves [91]. Cases of *P. marneffei* have been widely reported among visitors to Southeast Asia from countries outside the region [92–98]. There is also an increasing recognition of infection in India [99]. In Thailand, the northern provinces are the most affected [100].

10.7.2 Presentation

The most common clinical features of penicilliosis include fever, weight loss, nonproductive cough, lymphadenopathy, hepatosplenomegaly and anaemia. Many patients present with multiple papular skin lesions, which show a central necrotic umbilication and resemble molluscum contagiosum. These are often found on the face, neck, trunk and upper limbs [90]. Untreated, disseminated *P. marneffei* infection is almost invariably fatal. Chest radiographs may reveal interstitial lesions, cavities, fibrotic lesions and mass lesions [101,102].

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10.7.3 Diagnosis

The diagnosis can be made by direct microscopic examination of smears from skin or other lesions that reveal septate yeast forms. Culture of specimens from the bone marrow, lymph nodes, skin, and other infected sites shows a characteristic red colour on plates and diamorphism, which means that the fungus changes to a hyphal form at a lower temperature. Culture of these lesions is important, because other fungal infections, such as histoplasmosis and cryptococcus, may have similar clinical manifestations [90,103]. There are no widely available serological tests for this disease although antigen can be easily detected in the urine [104].

10.7.4 Treatment

- Penicilliosis should be treated with amphotericin B induction therapy for 2 weeks, followed by itraconazole 200 mg bd orally for 10 weeks and then maintenance therapy 200 mg once a day (category IV recommendation).

Penicillium marneffei is sensitive to commonly used antifungals [105]. In Thailand, the greatest treatment experience has been with intravenous amphotericin B 0.6 mg/kg per day for 2 weeks followed by oral itraconazole 200 mg bd po for a further 10 weeks. This regimen has a response rate of up to 95% and is well tolerated [106]. As discussed for other dimorphic fungi induction therapy with liposomal amphotericin B, 3 mg/kg/day intravenously, for the first 2 weeks should be considered in the UK (category IV recommendation).

Itraconazole has been recommended as lifelong suppressive therapy in patients infected with HIV who have completed successful treatment of *P. marneffei* infection [107]; however, there are some recent small case series suggesting that prophylaxis may be safely discontinued when immune reconstitution occurs on ART and individuals have sustained CD4 counts >100 cells/μL [108,109].

10.7.5 Prophylaxis

- Prophylaxis with itraconazole may be considered for travellers to endemic areas with CD4 counts <100 cells/μL.

It has been suggested, based on studies in other systemic mycoses [110] and a small trial in Thailand [111], that itraconazole 200 mg once a day orally be given as prophylaxis to travellers to the endemic areas who have CD4 counts <100 cells/μL [112].

10.7.6 Impact of HAART

There is little information on the impact of HAART on penicilliosis, but in Thailand the incidence appears low in individuals receiving HAART [113]. Most cases of penicilliosis occur at very low CD4 cell counts where HAART is indicated by current guidance. However, HAART should be commenced in all patients diagnosed with penicilliosis as soon as a clinical response is noted to treatment of penicilliosis.

There is little information on IRIS due to penicilliosis but as with other dimorphic fungi it is a possible presentation.

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11 Special considerations in pregnancy

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11.1 Background and epidemiology

AIDS-related complications are a common cause of maternal death worldwide and are responsible for a high proportion of maternal deaths in the developing world; they are a significant contributing cause of maternal death in the developed world, though the absolute numbers are small [1,2]. Their medical management is complicated by the requirement to balance the needs of the mother and the foetus, and the viability of the pregnancy itself.

- Opportunistic infections in HIV-seropositive pregnant women should be managed with close collaboration between HIV specialists, obstetricians, paediatricians and where possible, specialists in obstetric medicine and materno–foetal medicine (category IV recommendation).

Physiological changes in pregnancy are important to understand as they can impact on the interpretation of test results, clinical findings on examination and the pharmacokinetics of drugs used in pregnant women [1,3,4]. CD4 cell counts characteristically drop during pregnancy. Furthermore there is a shift from cell-mediated immunity (Th1 response) toward humoral immunity (Th2 response) which leads to an increased susceptibility to, and severity of, certain infectious diseases in pregnant women, irrespective of HIV infection, including toxoplasmosis, varicella and listeriosis [5]. There is an increase in cardiac output (30–50%), plasma volume (24–50%), red cell mass (20–30%) and glomerular filtration rate. Absorption of aerosolised medication may be affected by an increase in tidal volume and pulmonary volume. Placental transfer of drugs, increased renal clearance, altered gastrointestinal absorption and metabolism by the foetus may affect drug levels.

- Therapeutic drug monitoring (TDM) should always be considered due to altered drug pharmacokinetics in pregnancy, and the potential for complicated multiple interactions between antiretrovirals and many of the drugs used to treat opportunistic infections [3,6].

11.2 Diagnostic considerations in HIV-seropositive pregnant women

In general, pregnant women with symptoms suggestive of an AIDS-defining illness should be managed and investigated in the same way that they would be if they were not pregnant.

11.2.1 Radiology

There are detailed guidelines relating to the use of X-rays and other imaging techniques in pregnant women [7–11]. If opportunistic infection in the lung is suspected a chest X-ray may be carried out with little or no risk to the foetus as long as an abdominal shield is used and due consideration is given to exposure times and position of the X-ray. Plain abdominal X-rays should generally be avoided.

An ultrasound scan is a safe option for imaging of the abdomen. A direct CT scan of the foetus in the pregnant abdomen is contraindicated and, where possible, should be avoided. MRI scanning of the foetus and abdomen may be considered, although it is recommended to avoid them in the first trimester unless absolutely necessary.

CT scans of the brain, thorax or limbs of the mother may be carried out with minimal exposure to the foetus. Modern CT scanners have little radiation scatter to areas outside the scanner itself, so the main radiation scatter affecting the foetus during a thoracic CT scan would be internally within the body of the mother. The use of contrast with CT scanning is permitted. However, Gadolinium, which is used in MRI scanning, is not recommended as it has been found to be teratogenic in some animal studies, and should be avoided if possible.

Pulmonary embolus (PE) is a leading cause of maternal morbidity and death and suspected PEs need to be investigated and treated promptly. Ventilation and perfusion (VQ) scans, or in some situations limited 'perfusion' scans, are regarded as acceptable with suspected PE in pregnancy. CT pulmonary angiogram (CTPA) scans are also being used more and are becoming regarded by many as the investigation of choice for the diagnosis of PEs in pregnancy [7].

- When choosing imaging modality for the diagnosis of opportunistic infections in pregnant women consideration should be given to the need for a rapid diagnosis and the potential harm of the investigation. Discussion between HIV specialists, obstetricians and senior radiologist is recommended (category IV recommendation).

Lymph node biopsy, liver biopsy and lumbar puncture have no specific contraindications in pregnancy. Endoscopic procedures, including bronchoscopy and upper and lower GI endoscopy, may both also be undertaken if necessary [12].

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11.3 Diagnostic considerations for the foetus and newborn baby

11.3.1 Foetal monitoring

Where an opportunistic infection is being treated the foetus should be closely monitored, for example by serial high-resolution ultrasound scans and foetal cardiac monitoring, so that signs of disease, growth retardation, foetal distress or possible drug toxicity in the foetus can be detected early [1,13].

11.3.2 Vertical transmission of maternal opportunistic infections to the neonate

Congenital infections in the neonate have been described for a variety of opportunistic pathogens affecting the mother. These include *Mycobacterium tuberculosis* [14,15], cryptococcal infection [16,17], cytomegalovirus (CMV) [18], *Pneumocystis jirovecii* (PCP) [19,20] and toxoplasmosis [21,22]. Vertical transmission is generally assumed to be the route of infection, although in some cases it may not be clear whether the neonate acquired the infection *in utero* or during the perinatal or postnatal period.

- Neonates born to HIV-seropositive women should be assessed by a paediatrician, and where necessary actively screened, for congenital opportunistic infections. The placenta should also be examined histologically for signs of infection or disease (category IV recommendation).

11.4 Treatment considerations for specific opportunistic infections

(Letters in parentheses denote US Food and Drug Administration-assigned pregnancy categories [23].)

11.4.1 Pneumocystis jirovecii (PCP)

Therapeutic options are identical to non-pregnant patients.

- Trimethoprim-sulphamethoxazole (C/D) is the treatment of choice in pregnancy.

Alternative options are limited to: clindamycin (B) with primaquine (C); dapsone (C) with trimethoprim (C); or atovaquone (C) suspension. Clindamycin is generally considered safe in pregnancy, but primaquine can cause haemolysis. There are limited data on the use of dapsone in pregnancy; however, one review identified mild degrees of haemolysis [24]. Intravenous pentamidine is embryotoxic but not teratogenic, so should be used only if other options are not tolerated.

Steroids should be administered as per standard guidelines for the treatment of PCP in non-pregnant women.

Chemoprophylaxis for PCP should be prescribed to HIV-seropositive pregnant women as per guidelines for non-pregnant individuals. As for most drugs, avoidance of prescribing in the first trimester should be adhered to, other than in exceptional circumstances. It is important to remember that there is a false reduction in absolute CD4 cell counts during pregnancy, especially during the third trimester, and in such circumstances more emphasis should be put on the CD4 percentage as an indicator for the need to commence PCP or indeed any prophylaxis.

Trimethoprim-sulphamethoxazole (C/D) is the preferred prophylactic agent against PCP in pregnancy [25,26]. Concerns remain over the safety of this drug in the first trimester [27], and during this time an alternative agent could be used if indicated. Possible alternatives include once daily dapsone (C) or nebulised pentamidine (C). The dosing of these agents is the same as for non-pregnant individuals. Other alternatives to these agents include clindamycin (B) and primaquine (C) or atovaquone (C); however, data on their efficacy are not as clear as for the other agents, and data on their safety in pregnancy is not complete.

11.4.2 Cryptococcus neoformans

First-line therapy should be with liposomal amphotericin B (B). There are no reports of teratogenesis with liposomal amphotericin B in the literature [28].

The addition of flucytosine (C) to amphotericin B requires careful consideration. Teratogenic effects have been reported when used in rats at high doses [29]. However there are case reports of its use to treat cryptococcal meningitis during the second and third trimesters of pregnancy with healthy foetal outcomes [30,31]. Flucytosine should therefore only be used in combination with liposomal amphotericin B when potential benefits outweigh the risks and should be avoided during the first trimester whenever possible.

Most authorities recommend the use of fluconazole (C) during the consolidation phase of treatment for cryptococcal meningitis in non-pregnant individuals. High dose fluconazole treatment should be avoided during the early stages of pregnancy and substituted with liposomal amphotericin B. During the later stages of pregnancy the use of fluconazole as secondary prophylaxis may be considered (see below).

Voriconazole (D) use in rats has been strongly associated with teratogenicity and there are no reports in the literature of its use during pregnancy [32].

Congenital cryptococcosis has been reported, but appears to be rare [17].

11.4.3 Candida infections

Treatment of symptomatic vaginal candidiasis during pregnancy should be with topical agents, continued for at least 7 days.

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The first episode of oropharyngeal candidiasis may respond to topical treatment with nystatin suspension or amphotericin. Oral fluconazole (100 mg daily for 7 to 10 days) is probably more effective, with fewer relapses [33] but should be avoided during the first trimester of pregnancy and only used following failure of topical therapy later in pregnancy, as there are four case reports of an unusual cluster of congenital malformations (craniofacial and skeletal) when fluconazole has been used at high doses during the first trimester of pregnancy [34,35]. However, there are over 800 pregnancy outcomes recorded with exposure to low dose fluconazole ($\leq$ 150 mg) without an increased risk of malformations or miscarriage [36–40] and this provides a suitable alternative after the first trimester.

Oesophageal candidiasis requires systemic therapy. During the first trimester of pregnancy this should be with liposomal amphotericin B (B), for which there are no reports of teratogenesis in the literature [28]. During the later stages of pregnancy, oral fluconazole may be considered. Although caspofungin (C) and voriconazole (D) are effective treatments for oesophageal candidiasis, both are associated with foetal abnormalities in animal studies and are not recommended for use during pregnancy.

11.4.4 Toxoplasma gondii

First line treatment should be with sulphadiazine (B) and pyrimethamine (C). Although some animal studies have shown sulphadiazine to be teratogenic, there is no clear evidence of teratogenicity in humans [41]. If sulphadiazine is continued in the third trimester, there is a risk of neonatal haemolysis and methaemoglobinaemia. Although pyrimethamine is teratogenic in animals, causing cleft palate and neural tube defects, limited human data have not shown an increased risk of birth defects [21,41]. Pyrimethamine is a folate antagonist and should be prescribed with folinic acid.

Alternative options are clindamycin (B) with pyrimethamine (C) or atovaquone (C).

Secondary prophylaxis should be as for the non-pregnant.

All pregnant women should have *T. gondii* serological status checked. In the non-immunocompromised host, transmission of *T. gondii* to the foetus usually only occurs during acute infection. However, there have been case reports of transmission following reactivation in HIV-infected women with severe immunosuppression [21], although this is rare. Where there is evidence of acute infection or symptomatic reactivation in the mother, the foetus should be screened for evidence of perinatal transmission. Studies following up immunocompetent women with acute toxoplasmosis in pregnancy have not shown any conclusive evidence for the effectiveness of spiramycin, or sulphadiazine with pyrimethamine, to prevent congenital foetal infection [41,42].

11.4.5 Cytomegalovirus (CMV)

For systemic disease systemic therapy will be required. However, for patients with single site retinal disease, consideration may be given to providing local intravitreal therapy or implants to reduce foetal exposure to antivirals.

All the available antiviral agents, ganciclovir (C), valganciclovir (C), foscarnet (C) and cidofovir (C), are associated with congenital anomalies in rats and rabbits [43,44]. Ganciclovir is embryotoxic in rabbits and mice and teratogenic in rabbits. There is no published experience of valganciclovir in pregnancy, but the same concerns exist as for ganciclovir. Foscarnet is associated with an increased risk of skeletal anomalies in rats and rabbits, but there is no experience of its use in early human pregnancy. Due to the potential for renal toxicity, careful monitoring of amniotic fluid should be undertaken, especially in the second and third trimester, for oligohydramnios. Cidofovir also has shown evidence of embryotoxicity and teratogenicity in rats and rabbits, and there is no experience of using this drug in pregnancy.

Therefore, the most experience in clinical practice has been with intravenous ganciclovir, and either this agent or oral valganciclovir should be considered first line treatment for CMV disease in pregnancy [45,46].

Infants born to mothers with evidence of active CMV disease should be examined for evidence of congenital infection [18].

11.4.6 Herpes simplex virus (HSV) and varicella zoster virus (VZV)

Oral aciclovir (B) for either acute attacks or prophylaxis is indicated [47]. No adverse outcomes have been reported to the infant after *in utero* exposure to this drug [48,49]. There are fewer registry data available for famciclovir (B) or valaciclovir (B), and the manufacturers recommend their use only when potential benefits outweigh the risk [50].

11.4.7 Mycobacterium tuberculosis

HIV infection and tuberculosis are closely linked; HIV infection increases the risk of reactivation of latent TB by at least 20 fold [51,52]. Both infections most commonly occur in women of childbearing years and therefore, in communities with a high incidence of TB, HIV-seropositive pregnant women are at risk of developing symptomatic tuberculosis. TB and HIV are both independent risk factors for maternal mortality [14,53,54].

Maternal TB infection, not confined to the lymph nodes, has been linked to increased pregnancy complications, including

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low birth weight, preterm birth and intra-uterine growth retardation [55,56]. These complications are exacerbated when TB is diagnosed late or treatment is interrupted [55].

Investigation of pregnant women for tuberculosis should be the same as for non-pregnant adults. Although every effort should be made to obtain appropriate specimens for culture and sensitivity testing, treatment for suspected or probable TB should not be delayed, especially when managing an individual approaching the end of her pregnancy, to reduce the risk of transmitting *M. tuberculosis* to the neonate.

Treatment of TB should be the same as for the non-pregnant. All four first line drugs have a good safety profile in pregnancy and none appears to have teratogenic effects [57,58]. Isoniazid (C) causes hepatotoxicity in pregnant and non-pregnant adults, although one retrospective study, which was not statistically significant, has suggested that this is more common in pregnant women [59]. All pregnant women receiving isoniazid should be aware of potential hepatotoxicity and its symptoms, and their liver function should be checked if clinical symptoms deteriorate. Some authorities recommend regular monitoring of liver function during pregnancy. Pyridoxine should be used, as for all taking isoniazid.

Rifampicin (C) may increase the risk of haemorrhagic disease in neonates. Therefore neonates born to pregnant women taking rifampicin should be given vitamin K. Rifampicin is not known to be teratogenic.

Although pyrazinamide (C) is not recommended for use during pregnancy in the United States, both the WHO and International Union Against Tuberculosis and Lung Disease recommend its routine use for pregnant women being treated for TB [3]. There seems to be little evidence to suggest pyrazinamide is harmful in pregnancy and it should therefore be included in an initial anti-tuberculous regime. If pyrazinamide is omitted, the minimum duration of treatment is nine months.

Ethambutol (B) is not known to be harmful in pregnancy [60]. Ethambutol causes ocular toxicity in adults but visual problems have not been reported in neonates exposed in utero [3].

Despite FDA category B, there are no data on the use of rifabutin (B) in pregnancy. Rifampicin has been widely used in pregnancy and this drug is therefore preferred [60].

Managing TB in pregnant HIV-seropositive adults is complicated by drug interactions between antiretroviral therapy and antituberculous therapy, particularly rifampicin. Therapeutic drug monitoring (TDM) is therefore recommended for both antiretrovirals and antituberculous drugs when using the two together [27], especially in pregnancy. Rifampicin reduces the concentration of ritonavir-boosted protease inhibitors [61], risking loss of HIV virological control. Rifampicin and saquinavir/ritonavir coadministration can cause severe hepatocellular toxicity and is contraindicated [62]. There is insufficient evidence on the safety of rifabutin in pregnancy to recommend its use, but if reduced dose rifabutin (150 mg on alternate days or three times per week) is used with lopinavir/ritonavir, therapeutic drug monitoring should be used to monitor lopinavir levels in the pregnant woman. Rifampicin and efavirenz can be coadministered, but because of the concern of teratogenic effects of efavirenz in pregnancy it should be used with caution. There is increasing experience to suggest it can be considered after the first trimester. For those already on a regimen containing efavirenz, this should be continued, with dose alterations according to maternal weight and therapeutic drug monitoring. Another option would be to use a triple nucleoside regimen for pregnant women requiring anti-tuberculous therapy. Alternatively AZT monotherapy and planned caesarean section could be considered for those with an HIV VL $<10\,000$ copies/mL and able to discontinue antiretroviral therapy following delivery. Advice on drug interactions with antiretroviral therapy can be found in Section 11.6.

There is limited experience in the management of multi-drug-resistant TB (MDR-TB) during pregnancy and management should be in conjunction with a specialist in this field. Although there is limited experience with many second-line drugs in pregnancy, untreated TB, especially in those infected with HIV, will lead to increased maternal mortality and poor obstetric outcomes [53–56] and the risk of congenital and neonatal TB. There are a number of reports of the successful management of MDR-TB in pregnancy [63–65]. Pregnant individuals infected with MDR-TB should be transferred to a unit with expertise in this field.

11.4.8 Mycobacterium avium complex

Clarithromycin has been associated with birth defects in mice and rats, but two reviews failed to show an increase in major malformations in 265 women exposed in the first trimester [66,67]. There is no evidence for teratogenicity of azithromycin in animal studies. One hundred and twenty-three women were reported to the teratogenicity service in Toronto, Canada, having taken azithromycin during pregnancy (88 in the first trimester). No increase in malformations was seen when compared to those exposed to a non-teratogenic antibiotic [67].

11.5 Impact of HAART

There are no trial data examining the optimum time to start ART in the context of treating opportunistic infections in pregnancy. However, there is a consensus that in most situations ART should be started as soon as possible.

There have not been any publications describing immune reconstitution inflammatory syndrome (IRIS) relating to

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opportunistic infections in pregnancy for patients on HAART, but this must at least be a theoretical concern.

11.6 Potential antiretroviral drug interactions

Antiretroviral drugs, especially the NNRTIs and boosted PIs, have several important drug–drug interactions. The following are examples of drugs which are metabolized through cytochrome P450 enzyme system; rifampicin, rifabutin and azole antifungals. They are likely to have significant drug interactions, which may require change in drug dose, additional monitoring or coadministration should be avoided. As data and advice changes frequently, this information should always be interpreted in conjunction with the manufacturer's information (www.medicines.org.uk). Other useful web-based reference sources include the Liverpool HIV drug information website (www.hiv-druginteractions.org) and the Toronto Clinic website (www.hivclinic.ca/main/drugs_interact.html).

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12 Intensive care

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Keywords: intensive care unit, antiretroviral therapy

12.1 Background

From the start of the HIV epidemic, respiratory failure has been the most common indication for patients with HIV infection to be admitted to the intensive care unit (ICU). In the era of highly active antiretroviral therapy (HAART), *Pneumocystis jirovecii* pneumonia (PCP), bacterial pneumonia and tuberculosis continue to be significant causes of respiratory failure; however, admission to the ICU with non-HIV-associated respiratory causes, including emphysema and asthma, is increasingly encountered [1–3]. An emerging cause of respiratory failure requiring admission to the ICU is immune reconstitution inflammatory syndrome (IRIS) [4]. Non-respiratory causes, including renal and hepatic failure, cardiac disease, drug overdose and severe toxicity from HIV therapy are increasingly recognised [1–4].

Early in the HIV epidemic, HIV-seropositive patients with critical illnesses were deemed incurable. ICU mortality rates were high and long-term survival rates were low [5–7]. The majority of admissions to the ICU were patients with severe PCP. As a direct result of HAART, there has been a sustained reduction in HIV-associated morbidity and mortality. Several studies report improved outcomes for HIV-seropositive patients requiring admission to the ICU in the HAART era [1–3,8,9]. One recent study suggests that outcomes from ICU admission for HIV-seropositive patients are equivalent to those for the general medical (non-HIV-infected) population [3].

- HIV-seropositive patients should not be refused ICU admission based merely on the patient's HIV-serostatus (category IV recommendation).

Improved survival from HIV-associated PCP after 1996 has been shown to be independent of the use of HAART and likely reflect general improvements in the ICU management of acute lung injury (ALI) [10].

- All HIV-seropositive patients with ALI/acute respiratory distress syndrome (ARDS) who are mechanically ventilated should be managed using the same protocols for management of ALI/ARDS as among general populations – with low tidal volumes and controlled plateau pressures, for example using the ARDS Network guidelines [11] (category IV recommendation).

12.2 Antiretroviral therapy on the ICU

It is currently unclear whether starting HAART on the ICU confers improved outcome for HIV-seropositive patients admitted to the ICU [1,3,10]. In such patients, the short-term effect of HIV RNA level and CD4 cell count on mortality is unclear. Among HIV-seropositive patients already in receipt of HAART, there was no apparent improvement in survival when compared with HIV-seropositive patients not taking HAART [3]. The use of HAART in severely unwell HIV-seropositive patients is confounded by several issues, including drug absorption, requirements for dose modification in the presence of intercurrent renal- and hepatic-induced disease, drug–drug interactions (see Table 12.1), HAART-associated toxicity and IRIS. In some circumstances it may be more appropriate to change HIV therapy rather than dose modify. Advice should be sought from an HIV clinician and/or pharmacist prior to planned modification of HAART.

- Expert daily consultation between HIV and ICU physicians is essential in the management of critically-ill

Table 12.1 Potential ICU and antiretroviral drug interactions

Drug name	Interaction with antiretroviral	Action required
Antibiotics		
Clarithromycin	NNRTIs, PIs and boosted PIs can alter clarithromycin levels	See individual antiretroviral manufacturer's information
	Zidovudine levels may be decreased	Separate dose interval by 1–2 h
	Maraviroc likely to be increased	Reduce dose of maraviroc (150 mg od)
Rifabutin	Boosted PIs increase rifabutin levels	Reduce rifabutin dose (150 mg three times a week)
	NNRTIs can reduce rifabutin levels	Consider increasing rifabutin dose (450 mg od)
	Etravirine and rifabutin levels reduced when used together	Use with caution
Rifampicin	NNRTI levels reduced.	Increase dose of efavirenz (800 mg od depending on patient's weight)

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Table 12.1 (Contd.)

Drug name	Interaction with antiretroviral	Action required
		Contraindicated with etravirine and nevirapine (some units increase nevirapine dose)
	PI levels significantly reduced	Not recommended to be used together. Seek HIV specialist pharmacist advice
	Maraviroc levels reduced	Increase maraviroc dose (600 mg bd)
	Raltegravir levels reduced	Increase dose of raltegravir (800 mg bd)
Antifungals		
Amphotericin	Tenofovir	Caution – increased risk of renal toxicity with concurrent or recent use.
Itraconazole	Ritonavir increases itraconazole exposure	Avoid high doses of itraconazole Caution with boosted PIs – some PI levels increased
	Efavirenz, etravirine and nevirapine reduce itraconazole levels	Consider alternative, or increasing dose. Monitor clinical effect
	Maraviroc levels increased	Reduce maraviroc dose (150 mg BD)
Voriconazole	Efavirenz levels increased and voriconazole levels reduced	Not recommended to be used together. Seek HIV specialist pharmacist advice
	Etravirine and voriconazole levels are both increased	No dose adjustment required – monitor
	Voriconazole levels reduced by lopinavir/ritonavir	Not recommended to be used together. Seek HIV specialist pharmacist advice
Fluconazole	Zidovudine levels increased	Caution – monitor for adverse effects
	Nevirapine levels increased	Caution – monitor for adverse effects
Posaconazole	Efavirenz reduces posaconazole levels	Avoid combination unless benefit to patient outweighs risk
Caspofungin	Efavirenz and nevirapine reduce levels.	Increase caspofungin dose to 70 mg od, for those <80 kg
Acid-lowering agents		
H2 receptor blockers	Atazanavir levels reduced	Caution if used together. Temporal separation should be considered.
Proton pump inhibitors	Atazanavir levels significantly reduced	Not recommended to be used together. Seek HIV specialist pharmacist advice
	Saquinavir levels significantly increased by omeprazole	Not recommended to be used together. Seek HIV specialist pharmacist advice
	Raltegravir levels increased with proton pump inhibitors	Clinical significance unknown
Anticonvulsants		
	NNRTIs decrease levels of anticonvulsants such as carbamazepine, phenytoin and phenobarbital and anticonvulsants may reduce the levels of NNRTIs	Not recommended to be used together. Seek HIV specialist pharmacist advice. Use new anticonvulsant agents (e.g. vigabatrin, gabapentin)
	PIs and boosted PIs can increase levels of anticonvulsants such as carbamazepine, phenytoin and phenobarbital, as well as reduction in PI levels	Not recommended to be used together. Seek HIV specialist pharmacist advice. Use new anticonvulsant agents (e.g. vigabatrin, gabapentin)
HMG CoA reductase inhibitors		
Simvastatin	PIs and boosted PIs significantly increase simvastatin levels	Avoid simvastatin. Use low-dose pravastatin or low-dose atorvastatin. Dose titrate upwards. See individual drug manufacturer's literature
	NNRTIs reduce statin levels	See individual drug manufacturer's literature. Seek HIV specialist pharmacist advice
Others		
Warfarin	Ritonavir reduces effect of warfarin	Frequent INR monitoring initially
	Efavirenz and nevirapine have unpredictable effect on warfarin	Frequent INR monitoring initially
	Etravirine may increase warfarin effect	Frequent INR monitoring initially
Benzodiazepines	PIs increase diazepam levels	Manufacturers do not recommend coadministration. Use with caution and dose reduction
	NNRTIs decrease diazepam levels	Upward dose titration may be required
	PIs (boosted) increase midazolam levels	Not recommended to be used together. Seek HIV specialist pharmacist advice
	NNRTIs potentially decrease midazolam levels.	Upward dose titration required
Antiarrhythmics	Etravirine decreases levels of amiodarone and flecainide and other drugs in this class	Use with caution
	PIs can increase levels of amiodarone and flecainide	Not recommended to be used together. Seek HIV specialist pharmacist advice
	Efavirenz increases levels of amiodarone and flecainide.	Not recommended to be used together. Seek HIV specialist pharmacist advice

Antiretroviral drugs, especially the NNRTIs and boosted PIs, have several important drug–drug interactions. This table lists some examples of drug–drug interactions with antiretrovirals and drugs used in intensive care. As data and advice changes frequently, this information should always be interpreted in conjunction with the manufacturer's information (www.medicnes.org.uk). Other useful web-based reference sources include the Liverpool HIV drug information website (www.hiv-druginteractions.org) and the Toronto Clinic (www.hivclinic.ca/main/drugs_interact.html).

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HIV-seropositive patients admitted to the ICU. Additionally, the advice of a pharmacist with expertise of treatment of HIV-associated infection should be sought. In some cases this expertise will be obtained by transfer of the patient to a tertiary centre (category IV recommendation).

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13 A–Z of drugs used in the treatment of opportunist infections in HIV (Appendix 1)

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The information provided in this table (Appendix 1) should be read in conjunction with the pharmaceutical manufacturer's information as printed in the summary of product characteristics. (SmPC; www.medicines.org.uk). Readers should also take into consideration their own Trust's policies on Medicines Management, Intravenous Drug Administration, Antibiotics and their local formulary The Writing Committee takes no responsibility for information that may be incorrect at the time of accessing, and all data should be checked with additional reference sources.

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Appendix 1

Table A1

Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
Aciclovir Tablets: 200 mg, 400 mg, 800 mg Suspension: 200 mg/5 mL, 400 mg/5 mL Injection: 25 mg/mL	Herpes simplex: 200–400 mg orally five times a day for 5 days (or 5 mg/kg IV 8 hourly in more serious infection) duration of treatment adjusted according to response Prophylaxis of herpes simplex infections: 200–400 mg orally twice a day continuously Herpes zoster: 800 mg orally five times a day for 7–10 days (or 10 mg/kg IV 8 hourly) duration of treatment adjusted according to response. Following clinical improvement IV therapy may be switched to oral therapy Herpes encephalitis: 10 mg/kg IV three times a day for 7–14 days Unlicensed 15 mg/kg IV three times a day Progressive outer retinal necrosis (PORN): 10 mg/kg IV three times a day with foscarnet 90 mg/kg IV twice a day. Acute retinal necrosis Aciclovir followed by oral valaciclovir	Dose in renal impairment GFR (mL/min) Herpes zoster Oral 800 mg every 8 h <10 800 mg every 12 h Intravenous 25–50; 5–10 mg/kg every 12 h 10–25; 5–10 mg/kg every 24 h <10; 2.5–5 mg/kg every 24 h Caution when used in conjunction with other drugs, which are renally excreted	Use with caution in patients with serious hepatic dysfunction	Renal toxicity (particularly at high doses), watch patient for signs of dehydration and give additional fluids during IV administration, or high dose oral administration, neurological reactions (dizziness, confusional states, hallucinations), somnolence (usually in patients with renal impairment), skin rash, abnormal LFTs, nausea	Probenecid increases the half life and bioavailability of aciclovir.	B	Availability Wholesaler Other information Variable oral absorption. It is recommended that the state of hydration and the creatinine clearance should be evaluated before the administration of high dosages of aciclovir, especially in patients with reduced body mass Ensure infusion is administered as a slow IV infusion over a minimum of 1 h.	A-B
Albendazole Tablets: 200 mg	Microsporidiosis: 400 mg orally twice a day for at least 4 weeks Strongyloides: 400 mg orally twice daily for 3 days followed by a repeated dose after 3 weeks if necessary.	Dose as in normal renal function	Although there are no current recommendations for dose reduction in patients with moderate to severe hepatic dysfunction, since albendazole undergoes nearly 100% first-pass	Reversible increases in LFTs, leukopenia, pancytopenia, gastrointestinal disturbances (abdominal pain, nausea and vomiting), headache,	Albendazole is an inducer of cytochrome P450 isoenzymes, leading to possible reduced blood levels of other drugs metabolized via this route e.g.	C	Availability Named patient supply via IDIS or other licensed importer Other information Poor oral bioavailability. Take with fatty food to maximise oral absorption	B

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Table A1 (Contd.)

Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
			metabolism via the liver all patients with raised LFTS and receiving extended courses of albendazole should be monitored for leukopenia and pancytopenia	dizziness, alopecia, rash, fever	warfarin, oral contraceptives, protease inhibitors, NNRTIs etc.			
Amikacin Injection: 100 mg/2 mL 500 mg/2 mL 250 mg/mL	Mycobacterium avium complex and multi-drug resistant tuberculosis: 15 mg/kg IV daily given in two equally divided doses or as a single dose. The adult dose should not exceed 1.5 g/day nor be administered for a period longer than 10 days A maximum total adult dose of 15 g should not be exceeded	For dose in renal impairment GFR (mL/min) See SmPC for specific recommendations The SmPC for amikacin recommends that the serum creatinine concentration in mg/100 mL is multiplied by 9 and the resulting figure is used as the interval between doses. Renal handbook 20–50; 5–6 mg/kg every 12 h 10–20; 3–4 mg/kg every 24 h <10; 2 mg/kg every 24–48 h	No dosage adjustment currently recommended	Renal toxicity, ototoxicity (tinnitus, vertigo, partial reversible or irreversible deafness), skin rash, pyrexia, headache, paraesthesia, nausea and vomiting. If therapy is expected to last 7 days or more in patients with renal impairment, or 10 days in other patients, a pre-treatment audiogram should be obtained and repeated during therapy. Amikacin therapy should be stopped if tinnitus or subjective hearing loss develops.	Other nephrotoxic drugs e.g. foscarnet, cidofovir (absolutely contraindicated), other aminoglycosides, amphotericin, IV pentamidine and high dose loop diuretics.	C	Availability Wholesaler Other information Serum level monitoring required. See Trust specific guidelines For twice-daily dosing (and also for once a day dosing), a trough level should be taken prior to administering the 3rd or 4th dose. The dose or dosage interval should be modified if the trough level is >4–8 μg/mL. Further serum level monitoring should be performed twice weekly. The adult dose should not exceed 1.5 g/day nor be administered for a period longer than 10 days. A maximum total adult dose of 15 g should not be exceeded. The stopping date should be stated clearly on the patient's drug chart.	C
National Patient Safety Alert – Rapid Response Report **Caution when prescribing and administering amphotericin: doses refer to specific formulations**								
Amphotericin B Standard amphotericin is infrequently issued	Cryptococcal neoformans meningitis: For all indications the maximum daily dose must not exceed 1.5 mg/kg Amphotericin B 0.7–1 mg/kg IV once a day with	Dose in renal impairment GFR (mL/min) 20–50; Dose as in normal renal function 10–20; Dose as in normal renal function	No dosage adjustment currently recommended Therapy should be stopped if LFTs (elevated bromsulphalein, alkaline phosphatase and bilirubin) are abnormal	Infusion-related side effects: fevers, chills, nausea and vomiting, thrombophlebitis, myalgia, anaemia. Non-infusion-related: nephrotoxicity,	Additive toxicity with other nephrotoxic drugs e.g. foscarnet, IV pentamidine, aminoglycosides, cidofovir (absolutely contraindicated).	B	Availability Wholesaler Other information Adding 50 mg pethidine to the infusion bag will help with infusion-related side effects. Pre-treatment with	B

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	flucytosine 100 mg/kg/day (a test dose of 1 mg should be administered prior to the first infusion) N.B. An escalating dose of 0.25 mg/kg increasing up to 1 mg/kg over the initial 4 days is usually preferred. This is occasionally omitted in very severe infections In seriously ill patients the daily dose may be gradually increased to 1.5 mg/kg. Since amphotericin is excreted slowly, therapy may be given on alternate days in higher doses Other fungal infections e.g. 'azole'-resistant candida: 0.75–1 mg/kg IV once a day. Penicillium marneffei Acute infection in severely ill patients. Amphotericin 0.6 mg/kg/day IV for 2 weeks followed by itraconazole oral suspension 200 mg orally bd for at least 12 weeks total treatment Chronic suppressive therapy Itraconazole 200 mg od/bd as guided by therapeutic monitoring until immune restoration with ART	<10; 250 micrograms –1.5 mg/kg/every 24–36 hs		hypokalaemia, hypomagnesaemia, pancytopenia, abnormal LFTs If amphotericin therapy is interrupted for a period of longer than 7 days, therapy should be resumed by starting with the lowest level i.e. 0.25 mg/kg and increased gradually			paracetamol, IV hydrocortisone and IV chlorphenamine may also help Electrolyte supplements may be required Renal toxicity is related to cumulative dosage. Patients requiring extended treatment with doses over 5 g require intensive monitoring Lipid/liposomal formulations of amphotericin B have reduced incidence of renal toxicity (see below)	
National Patient Safety Alert – Rapid Response Report Caution when prescribing and administering amphotericin: doses refer to specific formulations								
Lipid amphotericin (Amphocil®)	Cryptococcal meningitis: 1 mg/kg IV once a day	Dose as in normal renal function	No dosage adjustment currently recommended.	Amphocil has reduced renal toxicity compared to	As above	B	Availability Wholesaler	E

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Table A1 (Contd.)

Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	increasing to 3–4 mg/kg IV once a day (higher doses up to 5–6 mg/kg may be used if required). A test dose of 1 mg should be administered prior to the first infusion (not necessary if the patient is transferring from conventional amphotericin B) Other fungal infections (e.g. 'azole'-resistant or disseminated candida): 1 mg/kg IV increasing to 3 mg/kg once a day, according to the infection severity.	In patients receiving dialysis, Amphocil should be administered at the end of each dialysis period		conventional amphotericin B, however, similar infusion-related side effects persist			Other information Use in patients with pre-existing renal impairment or if renal impairment develops during treatment with conventional amphotericin B Administration rate 1–20 mg/kg/h	
			National Patient Safety Alert – Rapid Response Report					
			Caution when prescribing and administering amphotericin: doses refer to specific formulations					
Liposomal amphotericin (Ambisome***®) Injection: 50 mg	Cryptococcal meningitis: 1 mg/kg IV increasing to 4 mg/kg IV once a day. A test dose should be administered prior to the first infusion (not necessary if transferring from an alternative amphotericin preparation). Histoplasma capsulatum: Moderately severe disseminated disease 1 mg/kg IV increasing to 3 mg/kg once a day for 14 days followed by maintenance with itraconazole 200 mg oral suspension three times daily then 200 mg orally twice daily for at least 12 months. CNS disease:	Dose as in normal renal function	No dosage adjustment currently recommended.	Reduced renal toxicity compared to conventional amphotericin B. Reduced incidence of infusion-related side effects compared to conventional amphotericin and Amphocil	As above. Ambisome therapy has been administered for as long as 3 months, with a cumulative amphotericin dose of 16.8 g without significant toxicity	B	Availability Wholesaler Other information Third-line treatment: use in patients with established renal impairment who are unable to tolerate conventional amphotericin B and Amphocil	E

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	Dose up to 5 mg/kg/day for 4–6 weeks. Visceral leishmaniasis: A total dose of 21–30 mg/kg of body weight given over 10–21 days Seek specialist advice Other fungal infections (e.g. 'azole' resistant candida): 1 mg/kg IV increasing to 3 mg/kg once a day, according to the infection severity. Doses should be titrated upwards from 1 mg/kg/day							
Atovaquone Suspension: 750 mg/5 mL	Mild to moderate PCP: 750 mg (5 mL) orally twice a day for 21 days. The preparation needs to be taken with high-fat food PCP prophylaxis (fourth-line): 750 mg (5 mL) orally twice a day Maintenance of toxoplasmosis (third-line): 1500 mg (10 mL) orally twice a day with pyrimethamine and folinic acid	Atovaquone has not been studied in patients with renal or hepatic disease. It is thought to be predominantly excreted unchanged in faeces	No dosage adjustment currently recommended	Rash, fever, abnormal LFTs, headache, nausea and vomiting, diarrhoea, neutropenia, anaemia	Care with any agent that may decrease GI transit time. Highly bound to plasma proteins (>99%): caution should be used when administering with other drugs that are highly protein bound and have a narrow therapeutic index e.g. phenytoin and warfarin Interaction reported with ritonavir when used as both PI or pharmacokinetic enhancer resulting in decreased atovaquone levels – caution	C	Availability Wholesaler Other information Poor bioavailability. Presence of food (particularly high fat) increases the absorption two to three fold. Doses for treatment of toxoplasmosis have not been defined with the liquid formulation. A dose of 750 mg four times daily with the tablet formulation was previously used; however, this is no longer available. The liquid formulation has higher bioavailability. Atovaquone liquid 750 mg twice daily should provide similar drug exposure	C
Azithromycin Capsules: 250 mg Suspension: 200 mg/5 mL	Atypical mycobacterial infections (MAI) or Mycobacterium Avium Complex (MAC): 500 mg orally once a day (as part	Dose as in normal renal function	Azithromycin is metabolized by the liver and excreted in the bile. There are no current data on the dosage adjustment	Gastrointestinal disturbances (abdominal pain, nausea, diarrhoea), rash, LFT elevations,	Azithromycin is an inhibitor of cytochrome P450 isoenzymes (but much less so than	B	Availability Wholesaler Other information Bioavailability of the capsule is increased if taken	A

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Table A1 (Contd.)

Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	of a combination regimen) MAC prophylaxis: 1250 mg once a week. Multi-drug resistant tuberculosis: 0.5–1 g orally once a day (as part of a combination regimen) Cryptospordium: 500 mg orally daily with paromomycin		in patients with moderate to severe hepatic dysfunction LFTs should be monitored closely in patients with hepatic dysfunction	hearing impairment (with high or prolonged doses)	other macrolides and used in preference to clarithromycin). There may be increased plasma levels of co-administered drugs metabolized by the same pathway e.g. theophylline, warfarin. Terfenadine and astemizole are contraindicated due to risk of cardiac arrhythmias Antacids impair absorption: azithromycin needs to be taken at least 1 h before or 2 h after antacids		on an empty stomach i.e. 1 h before or 2 h after food. The generic tablet formulation of azithromycin can be taken with food Azithromycin has been used as a last-line treatment for cryptosporidiosis and toxoplasmosis, but these are not routine indications	
Capreomycin Injection: 1 g	Multi-drug resistant tuberculosis: 1 g IM once a day (not more than 20 mg/kg) for 2–4 months, then 1 g 2–3 times each week (as part of a combination regimen)	See SmPC for specific recommendations on dose reduction with reduced creatinine	No dosage adjustment currently recommended; however, as capreomycin is used in combination with other hepatotoxic drugs, frequent monitoring of LFTS is suggested	Hypersensitivity reactions including urticaria and rashes, leukopenia or leukocytosis, rarely thrombocytopenia, changes in LFTs, nephrotoxicity, hearing loss, tinnitus, vertigo. As capreomycin is potentially ototoxic, audiometry and assessment of vestibular function should be performed before starting treatment and at regular intervals during treatment	Other nephrotoxic or ototoxic drugs e.g. amphotericin, foscarnet, aminoglycosides, cidofovir are (contraindicated)	C	Availability Wholesaler Other information Teratogenic in animals – contraindicated in pregnancy and breastfeeding. Reconstitution Administration Seek specialist pharmacist advice on part doses from a 1 g vial.	C
Caspofungin Injection: 50 mg, 70 mg	Invasive candidiasis Aspergillosis: Loading dose 70 mg IV on day 1 followed by 50 mg daily thereafter. In patients weighing more than 80 kg, 70 mg daily is	Dose as in normal renal function	For mild hepatic insufficiency (Child–Pugh score 5–6), no dosage adjustment is needed. For patients with moderate hepatic insufficiency (Child–Pugh score 7–9),	Anaemia, headache, tachycardia, phlebitis, dyspnea, abdominal pain, nausea, diarrhoea, vomiting rash, pruritus, sweating, fever elevated liver values (AST, ALT,	Caspofungin decreases tacrolimus trough concentrations by 26%. AUC of caspofungin is increased 35% by	C	Availability Wholesalers Other information Caspofungin plasma concentrations were on average 17–38% higher in women than in men, though	E

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	recommended for the loading and continuous therapy		caspofungin 35 mg daily is recommended. An initial 70 mg loading dose should be administered on Day 1. There is no clinical experience with severe hepatic insufficiency (Child–Pugh score greater than 9	alkaline phosphatase, bilirubin), increased serum creatinine, decreased haemoglobin	ciclosporin A. Trough concentrations of caspofungin are reduced by 30% with rifampicin at steady state (although caspofungin exposure may initially increase in the first few days with rifampicin). Caution – check SmPC for drug interactions with antiretrovirals The NNRTIs, efavirenz and nevirapine reduce caspofungin levels by 20-40% and increasing the dose of the latter (from 50–75 mg/day) is recommended		dose adjustment not thought necessary	
Cidofovir Injection: 375 mg/5 mL 1% cidofovir cream (special manufacturing)	CMV retinitis: 5 mg/kg IV once a week for 2 weeks (induction dose) followed by 5 mg/kg IV every 2 weeks (maintenance). Aciclovir-resistant HSV: 1% cidofovir cream	Cidofovir is contraindicated in patients with renal impairment serum creatinine $>133\,\mu mol/L$ or a $<$ 55 ml/min creatinine clearance <55 mL/min) or proteinuria ≥ 100 mg/dL (2 + proteinuria) Seek advice from a specialist pharmacist if patient's creatinine clearance is less than 55 mL/min Proteinuria as measured by urinalysis may be an early indicator of	The safety and efficacy of cidofovir has not been established in patients with hepatic disease	Nephrotoxicity, proteinuria, neutropenia, iritis, uveitis, decreased intraocular pressure, alopecia, and asthenia. Check renal function prior to receiving subsequent doses	Other nephrotoxic drugs contraindicated e.g. aminoglycosides, vancomycin, amphotericin, IV pentamidine, foscarnet. Probenecid – delays secretion of cidofovir into renal tubules reducing potential for renal toxicity Can cause decreases in intraocular pressure and impairment of vision – regular ophthalmological examination is recommended. Direct intraocular	C	Availability Wholesalers Cidofovir 1% cream – made by individual pharmacy production units (seek specialist HIV pharmacist advice) Other information Discuss all possible requests for cidofovir with specialist HIV pharmacist to allow as much time as possible to arrange for preparation. Not all units are able to prepare cidofovir on site Must be administered with IV hydration and oral probenecid according to a strict protocol, to avoid renal toxicity – see product literature for details.	E

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
		nephrotoxicity and should be used in conjunction with changes in creatinine clearance to monitor safety			injection is contraindicated		See SmPC for full details Probenecid administration is associated with a high incidence of nausea and vomiting and should be taken with food and an anti-emetic. Preparation of cidofovir should be done in a laminar flow biological safety cabinet.	
Ciprofloxacin Tablets: 100 mg, 250 mg, 500 mg Suspension: 250 mg/5 mL Injection: 100 mg/50 mL, 200 mg/100 mL, 400 mg/200 mL	Treatment of gastrointestinal infections (salmonella, shigella, campylobacter): 500 mg orally twice a day for 7–14 days (200 mg IV twice a day if the patient is vomiting) Salmonella septicaemia: Consider long-term or indefinite treatment particularly if the patient has AIDS. 250 mg twice a day for at least 3 months, following initial treatment course Atypical mycobacterial infections/multi-drug resistant tuberculosis: 500–750 mg orally twice a day (as part of a combination regimen) Pseudomonal infections: 500–750 mg orally twice a day or 200–400 mg IV twice a day	Dose in renal impairment GFR (mL/min) 20–50; Dose as in normal renal function <20; 50% of normal dose	No dosage adjustment necessary	Gastrointestinal disturbances, CNS effects (dizziness, headache, insomnia, fitting, euphoria – use in caution in patients with epilepsy), transient increases in LFTs, rash, taste disturbances, transient increases in serum creatinine and urea. Tendon damage (CSM warning) and severe anaphylaxis (rare)	Antacids, sucralfate, didanosine tablets, iron and zinc supplements will all decrease absorption Theophylline plasma levels increased – increased risk of convulsions Warfarin effect enhanced	C	Availability Wholesaler Other information Should not be taken at the same time of day as antacids, zinc or iron preparations Doses of ciprofloxacin and didanosine tablets should be separated by 2 h	A
Clarithromycin Tablets: 250 mg, 500 mg Suspension: 250 mg/5 mL Injection: 500 mg	Atypical mycobacterial infections (MAI) or Mycobacterium Avium Complex (MAC): 500 mg orally twice a day	Dose in renal impairment GFR (mL/min) 30–50 Dose as in normal renal function 20–30 Oral: 250–	Clarithromycin is both hepatically metabolized and renally excreted There are no recommendations on dosing in patients with	Gastrointestinal disturbances (nausea, dyspepsia, diarrhoea), rash, CNS disturbances (anxiety, headache, dizziness and confusion),	Clarithromycin is an inhibitor of cytochrome P450 isoenzymes. May cause raised levels of co-administered	C	Availability Wholesaler Other information Usually combined with ethambutol (rifabutin now less commonly used).	A

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Table A1 (Contd.)

Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	(as part of a combination regimen)	500 mg every 12–24 h. IV: 250–500 mg every 12 h <10; Oral: 250 mg every 12–24 h. IV: 250 mg every 12 h	moderate to severe liver disease and LFTs should be monitored	dysageusia, hepatic dysfunction.	drugs also metabolized via this route e.g. warfarin, theophylline, protease inhibitors, rifabutin. Terfenadine and astemizole contraindicated due to risk of cardiac arrhythmias. Azithromycin often used in preference.			
Clofazimine Capsules: 100 mg	Atypical mycobacterial infections (MAI) or Mycobacterium Avium Complex (MAC): Not recommended Second-line TB dose: 100 mg daily	No data available	No data available	Nausea, vomiting, diarrhoea, rash, pruritis, visual disturbance, conjunctival, sputum, tear, faeces discoloration	Limited data	C	Availability Idis pharmaceuticals	A
Clindamycin Capsules: 150 mg Injection: 150 mg/mL (2 mL or 4 mL)	PCP treatment: Intravenous: 600–900 mg IV every 6 or 8 h and primaquine 15–30 mg orally once daily for 21 days Oral: 300–450 mg orally four to three times daily and primaquine 15–30 mg orally once daily for 21 days Toxoplasmosis treatment: 600 mg orally or IV four times a day for 6 weeks (in combination with pyrimethamine and folinic acid) Toxoplasmosis maintenance: 1200 mg daily in divided doses (in combination with pyrimethamine and folinic acid)	Dose as in normal renal function Monitor closely in prolonged treatment courses	No data on dose reduction in hepatic dysfunction Monitor closely in prolonged treatment courses	Diarrhoea (common), pseudomembranous colitis (less common), rash, hepatotoxicity, bone marrow suppression (rare) Methaemoglobinaemia less likely if dose of primaquine 15 mg once daily is used	Potentiates the effects of neuromuscular blocking agents Antagonism has been demonstrated between clindamycin and erythromycin	B	Availability Wholesaler Other information Second-line agent for treatment of PCP (first line sulphamethoxazole) Second-line agent for treatment of toxoplasmosis (first line sulphadiazine)	Oral A

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
Sulphamethoxazole (Trimethoprim–sulphamethoxazole) Tablets: 480 mg, 960 mg Suspension: 240 mg/5 mL, 480 mg/5 mL Injection: 480 mg/5 mL	PCP treatment: Moderate to severe (as defined in Section 3): Intravenous trimethoprim 20 mg/kg and sulphamethoxazole 100 mg/kg in 3–4 divided doses for 3 days then reduce to trimethoprim 15 mg/kg and 75 mg/kg sulphamethoxazole every 24 h in 2–3 divided doses for 18 further days Mild to moderate Oral dose 1920 mg (2 × 960 mg tablets) orally TDS for 21 days Intravenous Trimethoprim 15 mg/kg and 75 mg/kg sulphamethoxazole every 24 h in 3 divided doses for 21 days. PCP or primary toxoplasmosis prophylaxis: In patients with a CD4 T cell count <200 and positive toxoplasma serology: 960 mg orally once a day or otherwise 480 mg orally once daily Secondary prophylaxis: 960 mg three times a week. Toxoplasmosis treatment: Third line (depending on availability of other agents) 60 mg/kg/day divided tid	Dose in renal impairment GFR (mL/min) 30–50; Dose as in normal renal function 15–30; 60 mg/kg/day in 2 divided doses <15; Not recommend	Intravenous sulphamethoxazole is contra-indicated in patients showing marked parenchymal damage	Rash (Stevens–Johnson syndrome: rare), nausea and vomiting, neutropenia, anaemia, abnormal LFTs, impaired renal function (at high doses), pancreatitis, hyperkalaemia, haemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficiency Sulphamethoxazole desensitization- see section 3.4.5	Additive toxicity with bone marrow suppressive agents e.g. ganciclovir, zidovudine Warfarin effect enhanced Effect of sulphonylureas enhanced Phenytoin – anti-folate effect and plasma concentration increased Ciclosporin – increased risk of nephrotoxicity Additive toxicity with other sulphonamides – (caution: sulphamethoxazole and sulphadiazine should not be co-prescribed)	C	Availability Wholesaler Other information Regular anti-emetics should be co-prescribed with high dose sulphamethoxazole Intravenous administration Dilute 1:25 in 0.9% saline or glucose 5% and infuse over 60–90 min The infusion should be prepared immediately before use and shaken thoroughly to ensure adequate mixing. The infusion should be checked for clarity during administration and discarded if cloudiness develops In fluid-restricted patients the infusion can be administered in higher concentrations of 5 mL diluted with 75 mL of glucose 5%, and infused over a maximum period of 1 h	A
Cycloserine Capsules: 250 mg	Multi-drug resistant tuberculosis (MDRTB): 250 mg twice a day orally	Dose in renal impairment GFR (mL/min)	No data on dose reduction in hepatic dysfunction	Mainly neurological including headache, dizziness, drowsiness,	Increased CNS toxicity with isoniazid	C	Availability Wholesaler Other information	B

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	initially for 2 weeks then increase to 500 mg orally twice a day (maximum) according to serum level	20–50; 250–500 mg every 12–24 h. Monitor blood levels weekly 10–20; 250–500 mg every 12–24 h. Monitor blood levels weekly <10; 250 mg every 24 h. Monitor blood levels weekly		tremor, convulsions (risk increased with alcohol), vertigo, confusion, psychosis, depression. Rash, megaloblastic anaemia, altered LFTs, heart failure at high doses reported	Increased phenytoin plasma concentration		Serum level monitoring required especially in renal impairment or if the daily dose exceeds 500 mg or if there are signs of toxicity. Blood concentration should not exceed 30 mg/litre Discontinue or reduce dose in symptoms of CNS toxicity. Contraindicated in patients with past medical history of fitting, chronic alcohol abuse or severe renal impairment.	
Dapsone Tablets: 50 mg, 100 mg	PCP treatment: 100 mg orally once a day (in combination with trimethoprim) for 14–21 days. PCP prophylaxis: 50–100 mg orally once a day When used with pyrimethamine (50–75 mg) once weekly protects against toxoplasmosis	Dose in renal impairment GFR (mL/min) 20–50; Dose as in normal renal function 10–20; Dose as in normal renal function, use with caution <10; 50–100 mg daily, use with caution	No data on dosage reduction Use with caution	Haemolytic anaemia, methaemoglobinaemia, peripheral neuropathy, rash, dapsone syndrome (rash with fever and eosinophilia) – discontinue treatment immediately, hepatitis, agranulocytosis	Additive toxicity with other drugs causing peripheral neuropathy e.g. isoniazid, stavudine Antacids and didanosine tablets prevent absorption (dapsone requires an acidic pH for absorption)	C	Availability Wholesaler Other information Test for G6PD deficiency May be some cross sensitivity between sulphamethoxazole and dapsone	A
Ethambutol Tablets: 100 mg, 400 mg	Mycobacterium tuberculosis: 15 mg/kg orally once a day for initial 2-month phase of treatment (as part of a combination regimen). 30 mg/kg 3 times a week or 50 mg/kg twice a week for D.O.T regimens. Atypical mycobacterial infections (MAI): 15 mg/kg orally once a day (as part of a combination regimen)	Dose in renal impairment GFR (mL/min) 20–50; Dose as in normal renal function 10–20; 15 mg/kg every 24–36 h, or 7.5–15 mg/day <10; 15 mg/kg every 48 h 5–7.5 mg/kg/day	No data on dose reduction in hepatic dysfunction	Visual disturbances (optic neuritis), gastrointestinal disturbances, rash	No significant drug interactions	B	Availability Wholesaler Other information Patients should undergo a full ophthalmological examination before starting ethambutol When treating MAI, ethambutol is usually combined with a macrolide antibiotic (clarithromycin or azithromycin), rifabutin is now less commonly used	A
	Not usually recommended as first line due to cost.	Dose in renal impairment	Dosage modification is not required for patients	Headache; nausea; rash; dizziness; confusion;	No significant drug interactions	B	Availability Wholesaler	B

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
Famciclovir Tablets: 250 mg, 500 mg, 750 mg	See aciclovir: Herpes simplex: 500 mg twice a day for 7 days. Herpes zoster: 500 mg orally three times a day for 10 days. Herpes simplex prophylaxis: 500 mg twice a day continuously.	GFR (mL/min) Herpes zoster: 30–39; 250 mg three times a day. 10–29; 125 mg three times a day. Herpes simplex: >40; 500 mg two times a day. 30–39; 250 mg two times a day 10–29; 125 mg two times a day	with well-compensated chronic liver disease There is no information on patients with decompensated liver disease	abdominal pain and fever have been reported in immunocompromised patients			Other information Famciclovir is a pro-drug of penciclovir.	
Fluconazole Capsules: 50 mg, 150 mg 200 mg Suspension: 50 mg/5 mL, 200 mg/5 mL Injection: 2 mg/mL (25, 100 mL)	Oropharyngeal candidiasis 50–100 mg once daily for 7–14 days Doses up to 200 mg orally once daily in patients with severe oral candida Oesophageal candidiasis 50–100 mg orally once daily for 14–21 days. In severe disease, dose up to 400 mg daily Prophylaxis of oral candida: 50 mg orally once a day Cryptococcal meningitis: Second-line initial therapy (when intolerant of amphotericin or mild infection) 400 mg orally/IV twice a day for up to 10 weeks (dose adjusted according to clinical/mycological response). Consolidation therapy (CNS/lung/disseminated): 400 mg orally daily 2 weeks after induction therapy and may be reduced to 200 mg daily	Dose in renal impairment GFR (mL/min) 11–50; Day 1: dose as normal followed by 50% of normal dose	Monitor and use with caution in patients with hepatic dysfunction No dosage recommendations are available	Gastrointestinal disturbances (nausea, diarrhoea, abdominal discomfort, flatulence); headache; rash	Fluconazole is metabolized by cytochrome P450 isoenzymes (although less so than other 'azoles') Caution Concomitant use of nevirapine has been shown to result in an increased exposure of nevirapine by 100% and potentially greater risk of hepatotoxicity Zidovudine levels may also be increased with fluconazole Increased risk of uveitis with rifabutin Rifampicin may decrease efficacy of fluconazole (to a lesser extent than with other 'azoles') Warfarin effect enhanced Plasma concentrations of sulphonylureas	C	Availability Wholesaler Other information Prophylaxis of oral candida should be avoided where possible to avoid fluconazole resistance. Patients on concurrent cytotoxic chemotherapy or corticosteroids may require prophylaxis Where possible treat oral candida with single dose fluconazole, reserve treatment courses for more severe infections Good oral bioavailability, therefore only use IV route if the oral route is not available or if there is evidence of malabsorption	Oral A IV C-D

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Table A1 (Contd.)

Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	after 10 weeks. Therapy may be discontinued following immune restoration with ART Cryptococcal pneumonia: 400 mg once daily for 10 weeks then 200 mg as maintenance dose Histoplasma capsulatum: Fluconazole 800 mg orally once daily for up to 12 months. Less effective than other second-line treatment with itraconazole				increased by fluconazole Phenytoin effect enhanced by fluconazole Terfenadine and astemizole contraindicated due to risk of arrhythmias			
Flucytosine Tablets: 500 mg Infusion: 2.5 g in 250 mL	Cryptococcal meningitis: 100 mg/kg/day IV in 4 divided doses (Should be used in combination with IV amphotericin B) Higher dose 150 mg/kg/day when used with fluconazole	Dose in renal impairment GFR (mL/min) 20–40; 50 mg/kg 12–hourly 10–20; 50 mg/kg 24–hourly <10; 50 mg/kg then dose according to levels.	Flucytosine is excreted primarily through the kidneys. No dosage recommendation is available in hepatic dysfunction	Nausea, vomiting, diarrhoea, rashes; less frequently confusion, hallucinations, convulsions, headache, sedation, altered LFTs; blood disorders including thrombocytopenia, leukopenia and aplastic anaemia reported	Additive toxicity with other myelosuppressive drugs e.g. ganciclovir, zidovudine, sulphamethoxazole	C	Availability IV –Wholesaler Tablets- available on named patient basis from Bell and Croyden Other information The recommended licensed dose is higher (200 mg/kg/day), although adequate effects are often obtained at lower doses Synergistic with IV amphotericin, therefore a daily dose of 100 mg/kg is usually sufficient Serum level monitoring is required – blood should be taken prior to the 5th dose for trough levels. Plasma concentration for optimal response = 35–50 mg/L. Should not be allowed to exceed 80 mg/L Each 250 mL bottle of IV flucytosine contains 34.5 mmols Na^+	E
Folinic acid (Calcium folinate)	Oral dose 30 mg when used with pyrimethamine	Dose as in normal renal function	No dosage reduction necessary	May decrease the efficacy of sulphamethoxazole	Folinic acid is contraindicated in	C	Availability Wholesalers	A

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Table A1 (Contd.)

Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
Tablets: 15 mg Injection: 15 mg/2 mL				(increased failure during PCP treatment has been reported) May diminish the effect of anti-epileptic medications; phenobarbital, primidone, phenytoin and ethosuximide and may increase the frequency of seizures	patients with pernicious anaemia or other anaemias due to vitamin B12 deficiency. Side effects are uncommon and include fever, insomnia and agitation		Other information Should always be co-prescribed with daily dosing of pyrimethamine	
Foscarnet Infusion: 24 mg/mL (250 mL, 500 mL Foscarnet cream 2% (unlicensed)	CMV retinitis infection: Induction treatment: 90 mg/kg IV 12 hourly for 14–21 days. Maintenance treatment: Initiate at 60 mg/kg IV once daily and if tolerated increase to 90–120 mg/kg IV once a day. Exact doses depend on renal function Direct intraocular injection: Usual injection prepared as 2400 mg/0.1 mL (0.05 mL injected). Injection frequency varied according to response CMV colitis, oesophagitis: Second line after ganciclovir Foscarnet IV 90 mg/kg twice daily for 14–28 days Resistant herpes simplex infection: 40 mg/kg IV 8–12 hourly for 2–3 weeks until healing Progressive outer retinal necrosis (PORN): Aciclovir 10 mg/kg IV	Dose in renal impairment GFR (mL/min) See SmPC for dosage reduction according to creatinine clearance Monitor renal function every second day during induction and weekly during maintenance	No dosage reduction required. Monitor LFTS	Renal toxicity; electrolyte disturbances (hypokalaemia, hypocalcaemia, (especially if used in conjunction with IV pentamidine) hypomagnesaemia); genital ulceration; abnormal LFTs; thrombophlebitis; anaemia; gastrointestinal disturbances; peripheral tingling; seizures; tremor; confusion Addition hydration oral or IV Irritation or genital ulceration can be prevented by ensuring careful washing of the genital area after micturation	Additive toxicity with other nephrotoxic drugs e.g. aminoglycosides, amphotericin, IV pentamidine Use with extreme caution Cidofovir contraindicated	C	Availability Wholesalers Other information Usually administered through a central venous line over 1–2 h. Diluted preparations can be administered peripherally. Slower infusion rates may reduce the risk of electrolyte disturbances. Patients should be encouraged to maintain a high level of hygiene to avoid genital ulceration Maintenance treatment with IV foscarnet now rarely used (if ever) due to the availability of newer, more convenient treatment options. Administration –via peripheral line requires dilution and preparation in pharmacy. Please contact the specialist pharmacist Foscarnet cream 2%. Available through Idis Pharmaceuticals	E

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Table A1 (Contd.)

Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	three times a day with foscarnet 90 mg/kg IV twice a day							
Ganciclovir Injection: 500 mg vial Intraocular implants	CMV retinitis, colitis, oesophagitis treatment: 5 mg/kg IV twice daily for 14–21 days IV maintenance treatment: 5 mg/kg IV once a day 7 days a week or 6 mg/kg IV once a day for 5 days each week Direct intraocular injection: Usual injection prepared as 2 mg/0.1 mL (0.1 mL injected). Injection frequency varied according to response	Dose in renal impairment GFR (mL/min) Induction IV dose: >70; 5 mg/kg every 12 h 50–69; 2.5 mg/kg every 12 h 25–49; 2.5 mg/kg/day 10–24; 1.25 mg/kg/day <10; 1.25 mg/kg/day after dialysis	No dose recommendations	Myelosuppression – neutropenia, thrombocytopenia; rash; CNS effects including seizures; abnormal LFTs	Additive toxicity with other myelosuppressive drugs e.g. zidovudine, sulphamethoxazole	C	Availability Wholesalers UK availability of ganciclovir implants Other information IV ganciclovir now rarely (if ever) used as a maintenance treatment, now that newer, more convenient treatment options are available. Ganciclovir is toxic and should be prepared in the pharmacy. Contact the specialist pharmacist to discuss preparation and availability If the solution comes into contact with the skin or mucosa, wash off immediately with soap and water	E
Isoniazid Tablets: 100 mg	Mycobacterium tuberculosis: 300 mg orally once a day, as part of a combination regime Or 15 mg/kg (max 900 mg) orally twice or three times a week for D.O.T regimens Prophylaxis of mycobacterium tuberculosis: 300 mg orally once a day	Dose in renal impairment GFR (mL/min) 20–50 Dose as in normal renal function 10–20 Dose as in normal renal function <10 100–200 mg daily suggested	Isoniazid should be used in caution in patients with pre-existing hepatic dysfunction. Monitor LFTs No dosage recommendations in hepatic dysfunction	Peripheral neuropathy; increased LFTs and hepatic necrosis; hypersensitivity reactions; rash; nausea; anaemia and thrombocytopenia	Antacids reduce absorption; increased CNS toxicity with cycloserine; enhanced phenytoin and carbamazepine effect; additive hepatic toxicity with carbamazepine; metabolism of ketoconazole increased Additive toxicity with other drugs causing peripheral neuropathy e.g. stavudine, dapsone	C	Availability Wholesalers Other information Pyridoxine should be give with isoniazid to prevent development of peripheral neuropathy (25 mg orally once a day prophylaxis, 50 mg orally three times a day for treatment) N.B. Rifinah contains rifampicin and isoniazid. Rifater contains rifampicin, isoniazid and pyrazinamide	A
Itraconazole Capsules 100 mg,	Oropharyngeal candidiasis: 200–400 mg	Dose as in normal renal function	Itraconazole is predominantly	Gastrointestinal disturbances (dyspepsia,	Antacids, H2 antagonists, proton	C	Availability Wholesalers	Oral Cap A

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
Oral liquid 10 mg/mL Intravenous infusion 10 mg/mL (The oral solution should always be used in preference to capsules due to the poor bioavailability of the capsules and therapeutic monitoring should always be performed to check levels)	orally daily for 5–14 days Other systemic fungal infections (aspergillosis, histoplasmosis, cryptococcosis, coccidioidomycosis) Up to 400 mg orally daily Fluconazole resistant oral or oesophageal candidiasis: 10–20 mL liquid orally twice a day for up to 14 days Oropharyngeal candidiasis: fluconazole resistance 200–400 mg orally daily for 5–14 days Other systemic fungal infections –second line options) (aspergillosis, histoplasmosis, cryptococcosis, coccidioidomycosis): Up to 400 mg orally daily Fluconazole resistant oral or oesophageal candidiasis:10–20 mL liquid orally twice a day for up to 14 days Histoplasmosis-disseminated: itraconazole 200 mg tds for 3 days then 200 mg twice a day for al least 12 months Pulmonary infection Acute infection: Itraconazole 200 mg orally once or twice a day for 6–12 weeks, may be more prolonged if CD4 count < 300	The IV formulation contains hydroxypropyl-β-cyclodextrin, which is contraindicated in patients with a creatinine clearance of less than 30	metabolized in the liver. The terminal half-life of itraconazole in cirrhotic patients may be prolonged and dosage adjustment should be considered	nausea, abdominal pain, constipation); headache; increases in LFTs; rash; dizziness CSM advice (heart failure) Caution in older patients, those receiving high doses or long courses or those taking negative inotropic drugs e.g. calcium channel blockers	pump inhibitors and didanosine tablets reduce absorption (acid environment required). Plasma concentration reduced by rifampicin and phenytoin; warfarin effect enhanced; terfenadine and astemizole contraindicated – risk of arrhythmias; delayed metabolism of vincristine; increased risk of myopathy with simvastatin – avoid concomitant use; increased plasma levels of sildenafil Itraconazole levels are reduced by both efavirenz and nevirapine and the dose of itraconazole may need to be increased if given with an NNRTI		Other information Liquid formulation has increased oral bioavailability. It also may have some local effect, therefore often useful for treating oesophageal candida Itraconazole does not have as good CNS penetration as fluconazole, therefore should only be used orally for treatment of cryptococcal meningitis in fluconazole resistant cases IV formulation –restricted in many hospitals –use oral where possible Take the capsules with or after food. The liquid formulation should be taken an hour before food or on an empty stomach TDM levels can be done in Bristol or Manchester	Liquid B IV D–E
Ivermectin Tablets: 3 mg	Strongyloides: 200 μg/kg orally per day for 2 days			Facial and peripheral oedema, tachycardia,		C	Availability Named patient basis via IDIS	C

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	Norwegian scabies: 200 μg/kg as a single dose orally	No data available on use in patients with renal dysfunction	No data available on use in patients with hepatic dysfunction	headache, N&V, abnormal LFTs Rash, and itching			or other licensed importer. Other information Should be taken an empty stomach with a glass of water	
Ketoconazole Tablets 200 mg	Oropharyngeal candidiasis: 200–400 mg orally daily for 5–14 days Fluconazole resistant candida: 200–400 mg orally daily for 5–14 days	No recommendations on dosing in renal dysfunction	Contraindicated in patients with acute or chronic liver disease	Increased LFTs and hepatitis; gastrointestinal effects (nausea, vomiting, abdominal pain); rash; headache; alopecia; thrombocytopenia; gynaecomastia	Antacids, H2 antagonists, proton pump inhibitors and didanosine tablets reduce absorption (acid environment required) Terfenadine and astemizole contraindicated – risk of arrhythmias; rifampicin, isoniazid and phenytoin decrease ketoconazole plasma levels; warfarin effect enhanced; terfenadine and astemizole contraindicated – risk of arrhythmias; indinavir metabolism inhibited; reduced plasma levels with nevirapine; inhibits metabolism of methylprednisolone and possible other corticosteroids; increased plasma sildenafil concentration	C	Availability Wholesalers Other information Tablets need to be taken with or after food	A
Moxifloxacin Tablets: 400 mg	Tuberculosis Oral 400 mg daily	No dosage reduction required	Insufficient data in patients with hepatic disease	Common side-effects include headache, dizziness, QT prolongation in patients with hypokalaemia, Nausea, vomiting,	See under ciprofloxacin; May prolong QT interval with the following drugs, which are	C	Availability Wholesalers Other Information Moxifloxacin is not active against *Pseudomonas aeruginosa*	A

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
				gastrointestinal and abdominal pains, diarrhoea, increase in transaminases	contraindicated: antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol), neuroleptics (such as phenothiazines, pimozide, sertindole, haloperidol, sultopride), tricyclic antidepressants, certain antimicrobials (erythromycin IV, pentamidine, antimalarials particularly halofantrine), certain antihistaminics (terfenadine, astemizole), others (cisapride) Check SmPC for full information May affect INR in patients receiving warfarin			
Nitazoxanide Tablets: 500 mg	Cryptosporidium Orally 500 mg BD for 3 days but may be required for up to 12 weeks In trials 1 g BD	No data available on use in patients with renal dysfunction	No data available on use in patients with hepatic dysfunction	Abdominal pain, vomiting, diarrhoea, headache and a green tint to urine and other bodily secretions	Nitazoxanide is highly bound to plasma protein (> 99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, as competition for binding sites may occur	B	Availability Named patient supply via Durbin or IDIS or other licensed importer Other information Should be taken with food. The nitazoxanide oral suspension is stable for 7 days once opened and contains 1.48 grams of sucrose per 5 mL (teaspoon). Individuals with diabetes may need to monitor their intake of sucrose	E

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
Ofloxacin Tablets: 200 mg, 400 mg Infusion solution: 2 mg/mL	Multi-drug resistant tuberculosis (MDRTB) and atypical mycobacterial infections: 400 mg orally twice a day, in combination with other agents	Dose in renal impairment GFR (mL/min) Normal initial dose then reduce to 200 mg twice a day <10; give initial dose then reduce to 200 mg daily	The excretion of ofloxacin may be reduced in patients with severe hepatic dysfunction	Gastrointestinal effects (nausea, vomiting, dyspepsia, abdominal pain); diarrhoea; headache; dizziness; sleep disorders; rash Less frequently drowsiness, restlessness, confusion, convulsions. Hypersensitivity and anaphylaxis	Increased risk of convulsions with NSAIDS; antacids, sucralfate and iron preparations reduce absorption; warfarin effect enhanced.	C	Availability Wholesalers Other information Use with caution in patients with history of epilepsy or seizures, in pregnancy/breastfeeding and in children or adolescents. Exposure to excessive sunlight should be avoided	A
Oseltamivir Capsules: 75 mg Suspension: 12 mg/mL	Influenza A treatment I(AV) 75 mg orally twice a day for 5 days followed by influenza vaccination Post-exposure prophylaxis 75 mg orally once daily for 10 days	Dose in renal impairment GFR (mL/min) 15–30; Dosage reduction of 50% advised	No data on dosage reduction in patients with hepatic dysfunction	Nausea, vomiting, abdominal pain, dyspepsia, diarrhoea; headache, fatigue, insomnia, dizziness; conjunctivitis, epistaxis; rash; very rarely hepatitis, Stevens–Johnson syndrome, and toxic epidermal necrolysis	Limited data. Low potential for drug interactions	C	Availability Wholesalers	B
Paromomycin Capsules: 250 mg	Cryptosporidial diarrhoea: Second-line therapy 500 mg orally four times or 1 g twice a day for 12 weeks. Often used in conjunction with azithromycin 500 mg daily	No data available Not thought to be absorbed through the gut; however, if extensive ulceration may lead to absorption and potential renal toxicity	No data on dosage reduction in patients with hepatic dysfunction	Gastrointestinal effects: abdominal cramps and nausea (both common), diarrhoea; renal toxicity (rare); ototoxicity (rare)	May affect warfarin	C	Availability Named patient supply via Durbin or IDIS or other licensed importer	B
Pentamidine Injection: 300 mg Nebulizer solution 300 mg	PCP treatment: 4 mg/kg IV once daily for 21 days PCP prophylaxis: 300 mg nebulized via Respirgard II every 4 weeks Less effective in subjects with CD4$<$100 and provides no cross prophylaxis cover against other OIs	Dose in renal impairment GFR (mL/min) 20–50; Dose as in normal renal function 10–20; Dose as in normal renal function <10; 4 mg/kg on alternate days to complete 14 doses	No data available on dosage reduction in patients with hepatic dysfunction Use with caution with possible dose reduction	Intravenous: Nephrotoxicity; postural hypotension; SIADH; hypocalcaemia; hypoglycaemia; hyperglycaemia; pancreatitis; facial flushing; nausea and vomiting; tachycardia; abnormal LFTs; dizziness; rash; leukopenia Caution Dysglycaemias may occur	Other nephrotoxic drugs e.g. aminoglycosides, amphotericin, foscarnet, cidofovir (contraindicated) Caution – hypocalcaemia especially with foscarnet Avoid other drugs that cause pancreatic toxicity e.g.	C	Availability Ready made nebulizer solution not always available. Use iv preparation Other information Intravenous reconstitution Ideally, intravenous solutions should be prepared in a fume cupboard to prevent exposure to staff and patients. Seek specialist pharmacist	C

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
				some time (14 days) after drug is stopped Blood glucose, HR and BP should be monitored regularly throughout the treatment period and for up to 1 week after stopping Inhaled: bronchospasm; cough; taste disturbances An inhaled beta-2-agonist should be administered prior to inhaled pentamidine	didanosine, sulphamethoxazole		advice and allow adequate time for preparation. Some units will require at least 3 working days. Dilute in 250 mL of 5% glucose and infuse over 1 h Administration Patients should be lying down whilst receiving the infusion Nebulized Ensure staff are trained in administration and handling. Nebulized pentamidine should be administered in a well-ventilated room away from other patients and staff	
Posaconazole Suspension: 40 mg/mL	Refractory invasive fungal infections: Invasive aspergillosis: Second line if intolerant or resistant to standard therapy Oral dose (oral suspension) 200 mg qid with food supplement or 400 mg twice a day Oropharyngeal candiasis: 200 mg as an initial dose on day 1 followed by 100 mg for 13 days	No dose adjustment required	Limited data in hepatic impairment and no recommendation can be made	Neutropenia, electrolyte imbalance, anorexia, paresthesia, dizziness, somnolence, headache, QTc/QT prolongation, abnormal ECG, palpitation, vomiting, nausea, abdominal pain, diarrhoea, dyspepsia, dry mouth, flatulence, elevated liver function tests (including ALT, AST, bilirubin, alkaline phosphatase, GGT) rash, pyrexia (fever), asthenia, fatigue	Posaconazole is metabolized via UDP glucuronidation, and is a substrate for p-glycoprotein as well as an inhibitor of CYP3A4 Posaconazole AUC is decreased 50% by rifabutin and phenytoin, and 40% by cimetidine Posaconazole increases AUC of rifabutin by 72%: avoid combination, or maintain vigilance for uveitis Posaconazole is expected to increase exposure of HIV PIs and NNRTIs, tacrolimus, ciclosporin,	C	Availability Wholesalers	E

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
					midazolam, digoxin, calcium antagonists, HMG-CoA reductase inhibitors (e.g. simvastatin, atorvastatin) Administration with terfenadine, astemizole, cisapride, pimozide, halofantrine and quinidine may increase risk of QT prolongation, and is contraindicated			
Prednisolone Tablets: 5 mg Soluble tablets: 5 mg Methyprednisolone 40 mg	PCP treatment: 40 mg orally twice a day for, days 1–5 40 mg orally once a day for days 6–10 20 mg orally once a day for days 11–21 Methylprednisolone PCP treatment: 75% of oral prednisolone dose	Dose as in normal renal function			Rifampicin may decrease prednisolone levels	C	Availability Wholesalers Other information Start corticosteroid as soon as possible and within 72 h of commencing specific anti-PCP treatment, if PaO2 $\leq$ 9.3 kPa ($\leq$ 70 mmHg)	A
Primaquine Tablets: 7.5 mg	PCP treatment: 30 mg orally once a day (in combination with clindamycin) for 24–21 days	Dose as in normal renal function	Metabolized via the liver. No data on dose reduction in hepatic dysfunction	Methaemoglobinaemia, nausea, vomiting, haemolytic anaemia Not to be used in patients with G6PD deficient	No specific drug interactions	C	Availability Named patient supply via Durbin or IDIS or other licensed importer Check for glucose-6-phosphate-dehydrogenase deficiency	B
Praziquantel Tablets: 500 mg	Schistosomiasis: Schistosoma haematobium, 20 mg/kg orally twice daily for 1 day Schistosoma japonicum, 60 mg/kg divided in two or three doses.	No dose adjustment in renal dysfunction likely	Hepatically metabolized No data available on dosage adjustment in hepatic dysfunction	Malaise, headache, dizziness, abdominal discomfort with or without nausea, rise in temperature and, rarely, urticaria	Few data Substrate of cytochrome P450, therefore drug interactions with strong inducers or inhibitors likely	B	Availability Merck Lipha Other information The tablets should be washed down unchewed with water during meals Treatment failures may be more common with HIV so follow eosinophil count and consider retreatment if not	B

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Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
							normalising. Important to speciate schistosomes by identification of eggs to ensure appropriate treatment	
Pyrimethamine Tablets: 25 mg	Toxoplasmosis treatment: A loading dose of 200 mg for day 1 then 75 mg (>50 kg) or orally once a day for up to 6 weeks (in combination with sulphadiazine or clindamycin) and folinic acid 15–30 mg daily Toxoplasmosis maintenance: 25 mg orally once a day (in combination with sulphadiazine or clindamycin) and folinic acid 15 mg daily PCP prophylaxis: 25 mg orally three times a week or 50 mg once each week (in combination with dapsone) Toxoplasmosis primary prophylaxis Should be considered for patients with CD4<200 and positive toxoplasma serology at 50 mg once each week	Dose in renal impairment GFR (mL/min) There are limited data in renal impairment as it is principally metabolized in the liver 20–50; Dose as in normal renal function 10–20; Dose as in normal renal function <10; Dose as in normal renal function	No data on specific dosage reduction in hepatically impaired patients Monitor LFTS	Neutropenia; thrombocytopenia; macrocytic anaemia; rash	Additive toxicity with other bone marrow suppressive drugs e.g. ganciclovir, sulphamethoxazole, and zidovudine	C	Availability Wholesalers Other information Folinic acid 15 mg orally once a day should always be co-prescribed with daily dosing of pyrimethamine	A
Rifabutin Capsules: 150 mg	Atypical mycobacterial infections and mycobacterium tuberculosis (as an alternative to rifamycin), DMAC: 300 mg orally once a day, as part of a combination regimen MAC prophylaxis: in	Dose in renal impairment GFR (mL/min) 30–50; Dose as in normal renal function <30; 150 mg once a day	Mild hepatic impairment does not require dosage adjustment. It should be used with caution in severe liver disease	Raised LFTs and jaundice; orange body secretions; uveitis (high doses); bone marrow suppression; arthralgia, gastrointestinal disturbances (nausea and vomiting)	Rifabutin is metabolized by and is an enzyme inducer of the cytochrome P450 isoenzyme system Plasma rifabutin concentrations increased by HIV PIs – dosage should be	B	Availability Wholesalers Other Information The dose of rifabutin is often modified when given in combination with protease inhibitors or non-nucleoside reverse transcriptase inhibitors	A

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	patients with CD4 counts less than 75 300 mg orally once daily but azithromycin preferred prophylaxis agent				reduced with concomitant boosted PIs or atazanavir Plasma rifabutin concentrations are decreased by NNRTIs. Increase dosage of rifabutin to 450 mg/day (unless PIs are also included in regimen) Plasma levels of co-administered drugs metabolized in the same way will be reduced e.g. warfarin, phenytoin, carbamazepine, protease inhibitors, oral contraceptives, and methadone Plasma concentration of rifabutin increased by fluconazole – risk of uveitis		(NNRTIs). Always check which antiretrovirals are being co-prescribed and modify doses – see SmPC. Consider TDM of rifabutin and antiretrovirals	
Rifampicin Capsules: 150 mg, 300 mg Infusion: 600 mg Syrup: 100 mg/5 mL Rifampicin contained within Rifater tablets Rifinah tablets	Mycobacterium tuberculosis, kansasii or some other atypical mycobacteria:: $<$50 kg – 450 mg orally once a day 50 kg and over – 600 mg orally once a day Or 600–900 mg orally three times a week or 600 mg orally twice a week as part of D.O.T regimens	Dose in renal impairment GFR (mL/min) 20–50; Dose as in normal renal function 10–20; Dose as in normal renal function $<$10; 50–100% of normal dose	A daily dose of 8 mg/kg should not be exceeded in liver impairment All patients should be monitored for changes in LFTs	Raised LFTs (rarely hepatitis and jaundice); gastrointestinal upset; skin reactions; orange body secretions; thrombocytopenia.	Rifampicin is a potent inducer of cytochrome P450 isoenzymes, leading to lowered plasma concentrations of co-administered drugs metabolized by the same pathway e.g. warfarin, ketoconazole, itraconazole, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, oral contraceptives, clarithromycin,	C	Availability Wholesalers Other Information Take on an empty stomach half to one hour prior to food N.B. Rifinah contains rifampicin and isoniazid. Rifater contains rifampicin, isoniazid and pyrazinamide Rifampicin is contraindicated/dose adjustments are usually required with protease inhibitors and NNRTIs. Always check which antiretrovirals are being co-prescribed	A

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					methadone, corticosteroids Rifampicin is contra indicated with saquinavir/ritonavir combinations due to increased risk of hepatotoxicity			
Sodium stibogluconate Injection: 100 mg/mL	Leishmania: Second line after liposomal amphotericin 20 mg/kg OD (max 850 mg) for at least 20 days	Should not be used in patients with significant renal impairment	No data	Approximately 1–2% of patients complain of nausea, vomiting and/or diarrhoea and a slightly higher number of abdominal pain Other common side-effects include anorexia, malaise, myalgia, arthralgia headache and lethargy ECG changes, including reduction in T-wave amplitude, T-wave inversion and QT prolongation have been observed. (see Special Warnings and Precautions for Use in current SmPC) Transient coughing immediately following injection was reported with varying frequency during several trials Intravenous injection of Pentostam may cause transient pain along the course of the vein and eventually thrombosis of that vein		C	Availability Other information IV injections to be given slowly over 5 min and stopped if coughing or substernal pain. Monitor using ECG Sodium stibogluconate solution should be filtered immediately prior to use	D
Sulphadiazine Tablets: 500 mg	Toxoplasmosis treatment: 1–2 g (15 mg/kg) orally four times a day for up to 6 weeks (in combination with pyrimethamine). Toxoplasmosis	Dose in renal impairment GFR (mL/min) 20–50; Dose as in normal renal function 10–20; Use 50% of		Rash (rarely Stevens–Johnson syndrome); haemolytic anaemia especially in patients with G6PD deficiency; other blood dyscrasias	Additive toxicity with other bone marrow suppressive and renally toxic drugs e.g. ganciclovir, zidovudine, and	B	Availability Commercial production of IV sulphadiazine has stopped and it is currently unavailable Other information	Not known

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Table A1 (Contd.)

Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	maintenance: 500 mg orally four times a day (or 1 g twice a day) in combination with pyrimethamine	dose and monitor levels. <10; Use 25% dose and monitor levels		(agranulocytosis, aplastic anaemia, leukopenia and thrombocytopenia); crystaluria; renal toxicity; raised LFTs (rarely hepatitis and jaundice); pancreatitis; gastrointestinal disturbances	trimetrexate Sulphadiazine is highly protein bound – effect of phenytoin and warfarin may be enhanced Caution: avoid other sulphonamides – do not co-prescribe sulphamethoxazole		Crystalluria can occur with sulphadiazine because of its low solubility. Adequate hydration will minimize the risk of this. A urine output of >1200 mL per day should be maintained throughout treatment. If crystalluria occurs stop treatment and alkalize the urine using bicarbonate	
Trimethoprim Tablets: 100 mg, 200 mg Suspension: 50 mg/5 mL	PCP treatment Trimethoprim 20 mg/kg/day orally in three divided doses and dapsone 100 mg orally once daily for 21 days	Dose in renal impairment GFR (mL/min) >25; Dose as in normal renal function 15–25; Dose as in normal renal function for 3 days, then 50% of dose every 18 h <15; Give 50% of normal dose every 24 h		Similar to sulphamethoxazole	See sulphamethoxazole	C	Availability Wholesalers Intravenous no longer available	A
Valaciclovir Tablets: 250 mg, 500 mg	Herpes simplex: 500 mg orally twice a day for 5 days (10 days if severe) Suppression of herpes simplex: 500 mg orally twice a day continuously. Herpes zoster: 1 g orally three times a day for 7 days.	Dose in renal impairment GFR (mL/min) 30–50; Dose as in normal renal function 15–30; Herpes simplex dose as in normal renal function. Herpes zoster 1 g every 12 h <15; Herpes simplex 500 mg daily Herpes zoster: 1 g every 24 h Herpes simplex suppression 500 mg daily	Clinical experience limited Caution with higher doses in patients with hepatic impairment	Gastrointestinal disturbances (nausea, vomiting, diarrhoea, abdominal pain); headache; rash; neurological reactions (dizziness, hallucinations, confusion, drowsiness)	Care with nephrotoxic drugs e.g. aminoglycosides, amphotericin, cidofovir, and foscarnet Probenecid reduces renal excretion	B	Availability Wholesalers –generic formulation available Other information Valaciclovir is the valine ester pro-drug of aciclovir. Higher oral bioavailability than aciclovir, therefore requires less frequent dosing. May be useful in patients with herpes simplex infections unresponsive to oral aciclovir, where aciclovir resistance is unproven Sometimes used following initiation with IV aciclovir in herpes zoster infection.	B
Valganciclovir Tablets: 450 mg	CMV retinitis treatment: 900 mg orally twice a day	Dose in renal impairment	No data in patients with hepatic impairment	Myelosuppression – neutropenia,	Additive toxicity with other	C	Availability Wholesalers	D

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Table A1 (Contd.)

Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	for 2–4 weeks CMV colitis or oesophagitis: valganciclovir may be considered if symptoms are not severe enough to prevent oral absorption (not licensed) CMV retinitis maintenance: 900 mg orally once a day	GFR (mL/min) 40–59; induction/ treatment 450 mg twice daily Maintenance/ prophylaxis 450 mg daily 25–39; Induction/ treatment 450vmg daily every 24 h 10–24; induction/ treatment 450 mg every 48 h Maintenance/ prophylaxis 450 mg twice weekly <10; Avoid		thrombocytopenia; rash; CNS effects including fitting, confusion, anxiety; abnormal LFTs; psychological effects including depression	myelosuppressive drugs e.g. sulphamethoxazole, zidovudine, and trimetrexate Didanosine increases plasma concentrations; probenecid delays renal excretion		Other information While patients are inpatient, more cost effective to use IV ganciclovir for treatment Doses should be taken with food Caution in handling valganciclovir is a potential teratogen and carcinogen and caution is advised for handling broken tablets; if broken tablets come into contact with skin or mucosa. Wash immediately with water	
Voriconazole Tablets: 50 mg 200 mg Suspension: 40 mg/mL Injection: 200 mg	Fluconazole-resistant serious invasive Candida (including C krusei Oral dose (tablets and suspension) >40 kg 400 mg (10 mL) every 12 h (for the first 24 h) then 200 mg twice daily <40 kg 200 mg (5 mL) every 12 h (for the first 24 h) then 100 mg twice daily Intravenous 6 mg/kg every 12 h (for the first 24 h) then 4 mg/kg twice a day Invasive pulmonary aspergillosis Acute therapy 6 mg/kg every 12 h (for the first 24 h) then 4 mg/kg twice a day for at least 7 days, followed by 200 mg orally twice a day to complete a total of	Dose in renal impairment GFR (mL/min) Oral dosing No dosage reduction in renal impairment IV infusion formulation <50; accumulation of the vehicle within the formulation occurs and the oral preparation should be used and serum creatinine carefully monitored in renally impaired patients	No dosage adjustment is required in patients with acute hepatic damage Monitor LFTs closely In patients with mild to moderate hepatic cirrhosis (Child–Pugh A and B) the standard loading dose should be used followed by half the maintenance dose. There is no data in patients with severe chronic hepatic cirrhosis	Influenza-like illness, gastroenteritis, thrombocytopenia, anaemia, leukopenia, pancytopenia, sinusitis, hypoglycaemia, hypokalaemia Anxiety, depression, hallucination Headache Dizziness, Visual disturbance Oedema peripheral Respiratory distress, pulmonary oedema, chest pain, abdominal pain, nausea, vomiting, diarrhoea, cholestatic jaundice, rash, erythema face oedema, pruritis	Co-administration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine is contraindicated since increased plasma concentrations of these medicinal products can lead to QT prolongation and rare occurrences of torsades de pointes Co-administration of voriconazole with rifampicin, carbamazepine and phenobarbital is contraindicated since these medicinal products are likely to decrease plasma voriconazole concentrations	D	Availability Wholesalers Other Information Oral dosing has 96% bioavailability	C

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Table A1 (Contd.)

Drug formulation	Dose and indication	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Side effects	Drug interactions	FDA pregnancy risk category	Other comments: Availability Other information	Cost
	12 weeks therapy Maintenance therapy Consider oral voriconazole or itraconazole in patients with low immunity				significantly Phenytoin, methadone and rifabutin levels may increase with voriconazole and may result in toxicity Check specific SmPC for specific drug interactions with antiretrovirals. Some examples include: When voriconazole and efavirenz are co-prescribed the dose of voriconazole should be increased to 400 mg every 12 h and efavirenz should be decreased to 300 mg every 24 h Low-dose ritonavir boosting may reduce levels of voriconazole – caution			
Zanamivir Inhalation powder: 5 mg/dose	Influenza A (IAV) treatment Second line: 10 mg twice daily (two puffs) by disk inhaler for 5 days Post-exposure prophylaxis 10 mg once daily for 10 days	No dosage reduction for inhalational formulation	No data on dosage reduction in patients with hepatic dysfunction.	Very rarely, bronchospasm respiratory impairment, angioedema, urticaria, and rash	Limited data Low potential for drug interactions	C	Availability Wholesalers	A

Drug Price					
Band	A	B	C	D	E
Price per day	0–£5	£5–20	£20–50	£50–100	>£100/day

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Appendix 2

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