British HIV Association guidelines on the management of opportunistic infection in people living with HIV: The clinical management of pulmonary opportunistic infections 2024

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1 Introduction

With improvements in the human immunodeficiency virus (HIV) testing and treatment cascade and reductions in the prevalence of advanced HIV, the incidence of 'classic' pulmonary opportunistic infections is lower, and so these infections are less frequently encountered by physicians. In addition, chronic lung diseases such as chronic obstructive pulmonary disease (COPD) have become more common in people living with HIV taking antiretroviral therapy (ART) [1].

HIV continues to alter the lung environment through the impact of persistent viral replication, inflammation, oxidative stress, alterations in the microbiome and the modifiable effects of cigarette smoking [1,2]. This means that the relative contribution of common community-acquired respiratory infections is greater and these can present with more severe disease necessitating different approaches to prevention compared with individuals without HIV. Accordingly, as well as pneumonia caused by *Pneumocystis jirovecii* (PCP), in these guidelines we consider bacterial pneumonia and influenza. Fungal pneumonias and cytomegalovirus (CMV), the incidence rates of which are low, are also considered. Each

section contains specific information about the epidemiology, presentation, treatment and prophylaxis of opportunistic infections.

A simple risk assessment allows the clinician to determine the likelihood that opportunistic infection is the cause of respiratory disease and that further pathogens may need to be considered. Relevant factors are listed in Box 1. In particular, lack of viral suppression and low CD4 counts increase the likelihood of the opportunistic infections seen commonly in the pre-ART era. Injecting drug use is associated in particular with increased risk of bacterial pneumonia and of TB.

Box 1 Risk factors for pulmonary opportunistic infection

Low CD4 T cell count
Detectable viral load
Non-adherence to ART or non-retention in HIV care
Non-adherence to opportunistic infection prophylaxis when indicated
Neutropenia
Use of prolonged courses of immune modulators (e.g. corticosteroids)
History of injecting drug use
Recent discharge from hospital or current hospital admission >5 days (for nosocomial infections)

Treatment is often started prior to laboratory confirmation of diagnosis. The intensity with which investigation is undertaken is usually determined by the risk assessment, the severity of the illness and the resources available locally. While empirical therapy (usually directed against bacterial pathogens) may be appropriate for individuals with CD4 counts >200 cells/mm^3, effort should be made to confirm a specific diagnosis, particularly in those who are more severely immunocompromised.

As evidence of drug toxicities, drug interactions, pregnancy safety and cost is constantly evolving, any specific drug and vaccine recommendations should be considered in association with the updated summary of product characteristics for that agent and other relevant sources of drug information. Drug interactions are common (for information see [3]).

These guidelines are intended to help physicians investigate and manage people living with HIV with a (suspected) pulmonary opportunistic infection. They are primarily intended to

assist practice in the UK and related healthcare systems. Their recommendations should be viewed as guidance; they are not designed to be restrictive nor should they challenge research into current practice. Similarly, although the aim of the writing group is to provide guidelines to optimise treatment, care needs to be individualised.

The prophylaxis and management of mycobacterial disease, including *Mycobacterium tuberculosis* and non-tuberculous mycobacteria (NTM), and COVID-19 in people living with HIV are not considered here. Tuberculosis (TB) is the focus of separate British HIV Association (BHIVA) guidelines [4] and NTM are reviewed in a separate chapter of the opportunistic infection guidelines [5]. Guidance on vaccination to prevent pneumococcal disease and influenza can be found in the BHIVA immunisation guidelines [6].

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

A full review of these guidelines is due by 2029, with interim updates only if recommendations need updating in line with new data.

2 Methods

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

Further details of the methodology can be found on the BHIVA website (https://www.bhiva.org/file/5d514ec9b503d/OI-guidelines-methods-general.pdf), including the use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess and grade the evidence. Good practice points (GPPs) are recommendations based on the clinical judgment and experience of the working group. GPPs emphasise an area of important clinical practice for which there is not, nor is there likely to be, any significant research evidence, but where the aspect of care is regarded as such sound clinical practice that healthcare professionals are unlikely to question it and where the alternative recommendation is deemed unacceptable.

3 Summary of recommendations

From Section 5.3 Diagnosis of PCP

- **PCP should be considered in any individual living with HIV who develops new-onset, or worsening of pre-existing, respiratory symptoms, with an abnormal chest radiograph (GPP)**
- **We recommend that PCP should be diagnosed by detection of *Pneumocystis* by immunofluorescence, histochemistry or PCR of induced sputum or BAL (Grade 1A).**
- **We recommend that people clinically suspected of having PCP with a negative result from sputum induction for *Pneumocystis* should be referred for bronchoscopy and BAL (Grade 1B).**
- **In symptomatic people with a normal chest radiograph, thoracic high-resolution computed tomography (CT) should be performed to assess the possibility of early PCP (GPP).**
- **We recommend that the detection of *P. jirovecii* by PCR in respiratory samples, in the absence of symptoms or signs of respiratory disease, should not *per se* trigger initiation of treatment for PCP (Grade 1B).**

From Section 5.3.4 Blood tests

- **We recommend measurement of serum (1-3)-β-D-glucan for people with suspected PCP (Grade 1B).**

From Section 5.5.2 First-line regimens for treatment of PCP

- **We recommend trimethoprim-sulfamethoxazole as the first-line treatment of choice for PCP of any severity (Grade 1A).**
- **We suggest that people who develop PCP despite taking trimethoprim-sulfamethoxazole as prophylaxis can be treated with standard high-dose trimethoprim-sulfamethoxazole (Grade 2C).**
- **We recommend that treatment should be continued in people living with HIV for 21 days (Grade 1B).**
- **We recommend that aerosolised pentamidine should not be used in the treatment of PCP because of its limited efficacy (Grade 1A).**

From Section 5.5.3 Adjunctive corticosteroids

- **We recommend that patients with laboratory proven or clinically suspected PCP and PaO_2 <9.3 kPa, or SaO_2 ≤92% at rest or falling by ≥3% on exercise, should receive adjunctive corticosteroids as soon as is possible and within 72 hours of starting anti-*Pneumocystis* treatment for maximal benefit (Grade 1A).**

From Section 5.5.4 Management of treatment failure

- **We suggest waiting at least 4 days before switching therapy in the absence of clinical improvement (Grade 2C).**
- **We suggest switching therapy for individuals who develop toxicity related to trimethoprim-sulfamethoxazole. Those with moderate-to-severe and mild-to-moderate PCP can be given oral primaquine combined with intravenous or oral clindamycin; those with mild disease can be given atovaquone (Grade 2B).**

From Section 5.6 When should ART be started when treating PCP?

- **We recommend that ART should be initiated, when possible, within 2 weeks of diagnosis of PCP (Grade 1B).**

From Section 5.8.2 Preventing a first episode of PCP (primary prophylaxis)

- **We recommend that all adults living with HIV with a CD4 count <200 cells/mm^3 should receive prophylaxis to prevent PCP (Grade 1A).**
- **We suggest that individuals who have a CD4 percentage of total lymphocytes <14% should be offered PCP prophylaxis (Grade 2B).**
- **We suggest that primary prophylaxis could be started in individuals with CD4 counts between 200 and 250 cells/mm^3 if ART is delayed or 3-monthly monitoring of CD4 count is not possible (Grade 2B).**
- **We recommend that prophylaxis to prevent PCP is not needed for individuals receiving sulfadiazine with pyrimethamine for treatment or secondary prevention of cerebral toxoplasmosis (Grade 1B).**
- **We recommend trimethoprim-sulfamethoxazole 960 mg (one double-strength tablet) or 480 mg (one single-strength tablet) once daily to prevent a first episode of PCP (Grade 1A).**

- **We recommend trimethoprim-sulfamethoxazole 960 mg three times a week as an alternative regimen to prevent a first episode of PCP (Grade 1B).**

From Section 5.8.3 Managing toxicity

- **We recommend that individuals who experience minor adverse reactions when taking trimethoprim-sulfamethoxazole as prophylaxis should continue trimethoprim-sulfamethoxazole if possible, with supportive care before discontinuation (Grade 1C).**
- **We recommend that if prophylaxis is discontinued because of a mild adverse reaction, restarting trimethoprim-sulfamethoxazole should be considered once the individual has recovered (Grade 1B).**
- **We suggest that trimethoprim-sulfamethoxazole may be restarted by gradually increasing the dose, which is known as 'desensitisation' (Grade 2A).**
- **We recommend that trimethoprim-sulfamethoxazole should be stopped in individuals with life-threatening reactions and not restarted (Grade 1C).**

From Section 5.8.4 Alterative regimens for primary and secondary prophylaxis

- **For individuals who cannot tolerate trimethoprim-sulfamethoxazole, we suggest nebulised pentamidine, dapsone, dapsone and pyrimethamine with folinic acid, or atovaquone (Grade 2A).**

From Section 5.8.5 When can primary prophylaxis for PCP be stopped?

- **We recommend that primary prophylaxis can be discontinued in individuals who have responded to ART with an increase in CD4 count to >200 cells/mm^3 for >3 months (Grade 1A).**
- **We recommend that primary prophylaxis can be stopped in individuals with CD4 counts between 100 and 200 cells/mm^3 if the plasma HIV load remains undetectable for 3–6 months (Grade 1B).**

From Section 5.8.6 Preventing recurrence of PCP (secondary prophylaxis)

- **We recommend that secondary prophylaxis with trimethoprim-sulfamethoxazole should be started immediately after completing treatment for PCP and continued until immune reconstitution occurs in response to commencing ART (Grade 1A).**

From Section 6.1 Background and epidemiology of bacterial pneumonia

- **We recommend that pneumonia should be considered a possible indicator of HIV infection and an opportunity for HIV testing in line with testing guidelines [79] (Grade 1C).**
- **Gram-negative pathogens should be considered especially likely in people living with HIV who develop pneumonia when hospitalised (GPP).**

From Section 6.2 Presentation of bacterial pneumonia

- **For people requiring hospitalisation, a blood culture should be obtained before starting antimicrobials and urine antigen testing for *Pneumococcus* and *Legionella* should be performed (GPP).**

From Section 6.3 Treatment of bacterial pneumonia

- **We recommend that people living with HIV with community-acquired bacterial pneumonia should be treated in the same way as people without HIV and as outlined in community-acquired pneumonia guidelines (Grade 1D).**

From Section 6.4 Follow-up of bacterial pneumonia

- **We suggest that people living with HIV with bacterial pneumonia should have a follow-up chest radiograph if clinical features have not resolved, they are aged over 50 or are smokers (Grade 2C).**

From Section 6.5 Prophylaxis of bacterial pneumonia

- **We recommend that people living with HIV should be offered pneumococcal vaccination according to national guidelines (Grade 1C).**
- **We recommend that people living with HIV who have bacterial pneumonia and are current smokers should be offered a smoking cessation intervention (Grade 1C).**

From Section 6.6 Starting ART after an episode of bacterial pneumonia

- **We recommend that ART should be started within 2 weeks of initiating pneumonia therapy in those not already on ART (Grade 1B).**

From Section 7.2 Diagnosis of influenza

- **Influenza and COVID-19 tests should be performed in people living with HIV with an influenza-like syndrome, pneumonia or exacerbation of a chronic respiratory syndrome (e.g. asthma or COPD) during periods when influenza is circulating, unless national guidance during pandemics suggests an alternative strategy for the general population (GPP).**

From 7.3 Treatment of influenza

- **We suggest that people living with HIV should be treated when influenza is detected and can start treatment within 48 hours of symptom onset (Grade 2D).**
- **We suggest that people living with HIV should receive the NI oseltamivir (assuming that the majority of circulating strains in a given influenza season show susceptibility) (Grade 2D).**
- **We suggest that for individuals with significant immunosuppression (CD4 count <200 cells/mm^3), treatment may be administered if afebrile or if symptoms have been present for more than 48 hours (Grade 2D).**
- **We suggest that when people living with HIV continue to shed virus or show no symptomatic improvement 7–10 days after initiation of antivirals for influenza A, therapy should be switched to an alternative antiviral based on current predicted sensitivity with testing of the strain for NI resistance if available (Grade 2D)**.

From Section 7.4 Prophylaxis for influenza

- **We recommend that people living with HIV should be offered annual influenza vaccination with a parenteral non-replicating vaccine, and this includes pregnant women living with HIV (Grade 1A) as per the BHIVA immunisation guidelines.**

From Section 8.3 Diagnosis of cryptococcal disease

- **We recommend that pulmonary cryptococcosis should be diagnosed by culture or microscopic identification of yeast in a biopsy specimen or BAL or pleural fluid (Grade 1C).**
- **We recommend serum cryptococcal antigen testing for all individuals with suspected pulmonary cryptococcosis and if positive a lumbar puncture should be offered to exclude cryptococcal meningitis (Grade 1C).**

From Section 8.4 Treatment of cryptococcal disease

- **We recommend that pulmonary cryptococcosis should be treated in the same way as CNS infection (Grade 1C), unless focal and not associated with hypoxia or a positive CSF examination.**
- **We suggest that pulmonary cryptococcosis, when focal and not associated with hypoxia or a positive CSF examination, may be treated initially with fluconazole 400 mg daily (Grade 2C).**

From Section 8.5 Prophylaxis for cryptococcal disease

- **We suggest that secondary prophylaxis can be discontinued after 1 year of cryptococcal therapy when the CD4 count is >100 cells/mm^3 and the individual has received ART with an undetectable HIV viral load for >3 months (Grade 2B).**

From Section 9.3 Diagnosis of aspergillosis

- **We recommend that aspergillosis should be diagnosed by a combination of clinical, radiological and microbiological features. A histological sample can help exclude other conditions and increase the accuracy of diagnosis (Grade 1A).**
- **We recommend that special fungal staining such as KOH staining of sputum or BAL fluid and Grocott–Gomori methenamine silver or equivalent staining of biopsy specimens should be performed on all respiratory specimens from people living with HIV with pulmonary syndromes of undetermined aetiology (Grade 1C).**
- **We recommend that serum galactomannan can be used to aid the diagnosis of invasive pulmonary aspergillosis (Grade 1C).**
- **We suggest in cases being investigated for chronic pulmonary aspergillosis, BAL**

galactomannan or PCR can be combined with *Aspergillus*-specific IgG (Grade 2C).

- **For subacute IA, we suggest that BAL galactomannan or PCR can supplement other tests (Grade 2C).**
- **We suggest that fungal culture should be requested on all samples as the definitive method of proving speciation (Grade 2B).**

From Section 9.4 Treatment of aspergillosis

- **We recommend primary therapy with voriconazole for invasive or chronic pulmonary aspergillosis in people living with HIV (Grade 1B).**

From Section 9.5 Prophylaxis for aspergillosis

- **We recommend that routine prophylaxis for pulmonary aspergillosis is not warranted (Grade 1C).**

From Section 10.3 Diagnosis of CMV

- **We recommend that diagnosis of CMV pneumonitis requires a biopsy specimen to provide definitive evidence of pulmonary involvement in association with a compatible clinical syndrome (Grade 1C).**

From Section 10.4 Treatment of CMV

- **We recommend that the majority of individuals in whom microbiological tests on BAL fluid, or biopsy, demonstrate CMV should not receive treatment for CMV (Grade 1C).**
- **In cases with a compatible clinical syndrome and consistent microbiological or CMV PCR findings in the absence of any other pathogens, we recommend that anti-CMV treatment should be considered (Grade 1C).**
- **In individuals co-infected with other pathogens, it is reasonable to start by treating the co-pathogen first and to treat the CMV only if there is a failure of clinical response (Grade 1C).**
- **We recommend ganciclovir as standard therapy for CMV pneumonitis (Grade 1C).**

From Section 10.5 Prophylaxis for CMV

- **We recommend that valganciclovir may be considered as primary prophylaxis in selected people with persistent immunosuppression and detectable CMV DNA, or as secondary prophylaxis in those with relapse of CMV pneumonia after appropriate primary therapy (Grade 1C).**

4 Auditable outcomes

- Proportion of people with suspected PCP, for whom the diagnosis is confirmed by demonstration of the organism (by histochemical staining) or detection of *P. jirovecii* DNA (by polymerase chain reaction [PCR]) in bronchoalveolar lavage (BAL) fluid or induced sputum.
- Proportion of people receiving appropriate treatment for *P. jirovecii* in line with BHIVA guidelines.
- Proportion of people who commence ART within 2 weeks of a diagnosis of PCP.
- Proportion of people who have been vaccinated against pneumococcus.
- Proportion of smokers who have been offered help with smoking cessation after pneumonia.
- Proportion of people living with HIV with an influenza-like syndrome, pneumonia or exacerbation of a chronic respiratory syndrome (e.g. asthma or COPD) during periods when influenza is circulating who are offered an upper respiratory nucleic acid amplification test for influenza and SARS-CoV-2 or PCR with an extended respiratory panel including these viruses.
- Proportion of people living with HIV receiving a neuraminidase inhibitor (NI) for influenza in line with national guidance.
- Proportion of people living with HIV who are offered annual influenza vaccination.

5 *Pneumocystis* pneumonia (PCP)

5.1 Background and epidemiology of *Pneumocystis*

Pneumocystis is a host-specific opportunistic pathogen found in humans and in many mammals [7]. In humans immunocompromised by HIV infection and other conditions, *P. jirovecii* causes PCP. *P. carinii* refers to the species of *Pneumocystis* that causes PCP in rats. Primary infection with *P. jirovecii* occurs in early life and is either asymptomatic or is associated with mild upper respiratory tract symptoms [8,9]. Serological studies show that most healthy children, regardless of HIV status, are exposed to *Pneumocystis* in the first 6 months of life [7-9].

It is thought that all individuals are repeatedly exposed to *Pneumocystis* throughout life. Animal studies in rats and reports of case clusters in immunodeficient/immunosuppressed humans suggest air-borne transmission of *Pneumocystis* [7].

Before the widespread use of PCP prophylaxis and ART, PCP occurred in up to 80% of people living with HIV and had a mortality of up to 40% despite treatment [10]. Most (but not all) cases of PCP occurred in patients with CD4 counts <200 cells/mm^3. In the pre-ART era, other factors were associated with risk of PCP including a previous episode of PCP, unintentional significant weight loss, oropharyngeal candidiasis, CD4 percentage <14% and high plasma HIV RNA levels [11,12]. Although less often applicable in contemporary care, these factors may still be applicable to some people who are diagnosed late or those not retained in care. The incidence of PCP has fallen markedly with widespread availability and use of PCP prophylaxis and ART. PCP now occurs largely in those who are unaware of their HIV status, who lack access to medical care or who are not taking ART and/or PCP prophylaxis consistently [13]. However, it is important to note that while PCP risk increases with falling CD4 count it can still occur at CD4 counts >200 cells/mm^3.

5.2 Clinical presentation of PCP

The presenting symptoms of PCP [14] are non-specific and have a broad infectious and non-infectious differential diagnosis. The most common presentation is with a subacute onset of progressive breathlessness on exertion, fever and non-productive cough. An inability to inhale deeply, that is not due to chest pain, is frequently reported [14]. Sputum production is rare; haemoptysis is not a feature. Typically, symptoms worsen over 3–8 weeks. In

contrast to the presentation of PCP in people without HIV, a rapidly progressive course with deterioration over 7–10 days is rare in people living with HIV [15].

Clinical examination in mild cases of PCP may be normal. With more severe disease, signs of respiratory distress may be observed, with increased respiratory rate and heart rate, use of accessory muscles of respiration and central cyanosis [14]. Examination of the chest is usually normal; in some cases, auscultation reveals fine end-inspiratory crackles. Arterial oxygen saturation (SaO_2) may be reduced, or normal in early disease. In people with suspected PCP but minimal symptoms, oxygen desaturation on exercise may indicate significant disease; although not specific for PCP, it is a characteristic feature. Stigmata of immunodeficiency may also be observed, including seborrhoeic dermatitis, extra-genital molluscum contagiosum, cutaneous Kaposi's sarcoma, oral candidiasis and oral hairy leucoplakia [14]. Extra-pulmonary *Pneumocystis* infection is rare, though can occur in any organ and is associated with advanced HIV infection (low CD4 counts) and use of nebulised pentamidine prophylaxis for PCP [14].

5.3 Diagnosis of PCP

Recommendations

- **PCP should be considered in any individual living with HIV who develops new-onset, or worsening of pre-existing, respiratory symptoms, with an abnormal chest radiograph (GPP).**
- **We recommend that PCP should be diagnosed by detection of *Pneumocystis* by immunofluorescence, histochemistry or PCR of induced sputum or BAL (Grade 1A).**
- **We recommend that people clinically suspected of having PCP with a negative result from sputum induction for *Pneumocystis* should be referred for bronchoscopy and BAL (Grade 1B).**
- **In symptomatic people with a normal chest radiograph, thoracic high-resolution computed tomography (CT) should be performed to assess the possibility of early PCP (GPP).**
- **We recommend that the detection of *P. jirovecii* by PCR in respiratory samples, in the absence of symptoms or signs of respiratory disease, should not *per se* trigger initiation of treatment for PCP (Grade 1B).**

5.3.1 Chest radiography

Radiographic abnormalities include bilateral diffuse interstitial infiltrates extending out from the perihilar region, often with subpleural sparing [7,14]. The chest radiograph may be normal initially, despite progressive respiratory symptoms. More confluent alveolar shadowing ('white out'), with relative sparing of the costophrenic angles and apices, is observed in individuals with rapidly progressive disease or those who present late in the course of their illness [14]. These chest radiograph abnormalities are sensitive for detecting PCP but are non-specific as they are also seen in viral, bacterial, mycobacterial and other fungal infections, as well as in non-infectious conditions including pulmonary Kaposi's sarcoma and non-specific interstitial pneumonitis. Atypical appearances include mediastinal lymphadenopathy, pleural effusion, unilateral infiltrates, cystic air spaces, pneumatoceles, nodules and pneumothoraces [7,14].

5.3.2 High-resolution CT

Thoracic high-resolution CT is useful in evaluating immunodeficient people with a pneumonitis and a normal or equivocal chest radiograph. Ground glass opacities, often 'geographic', are typical of PCP but are also observed in pneumonitis caused by viral (e.g. CMV and community-acquired respiratory viruses such as influenza A virus) or fungal (e.g. *Talaromyces marneffei*) pathogens, as well as in hypersensitivity pneumonitis, occult diffuse alveolar haemorrhage, pulmonary fibrosis and pulmonary oedema [7,14]. Thoracic high-resolution CT also identifies people with normal lung parenchymal appearances, who are unlikely to have PCP and who can be monitored without starting anti-*Pneumocystis* treatment.

5.3.3 Measures of oxygenation

In individuals with PCP, reduced blood oxygenation is a frequent finding [7,14]. The degree of hypoxaemia (measured as arterial partial pressure of oxygen [PaO_2]) or an increased alveolar–arterial oxygen gradient, or low SaO_2 measured with a transcutaneous oximeter, is used to evaluate disease severity (Table 1) and monitor progression. Although SaO_2 does not always accurately reflect PaO_2, there are considerable practical advantages in using this as a first measure of oxygenation rather than an arterial blood gas result. Indications for arterial blood gas measurement include sepsis syndrome, widespread changes on chest imaging and SaO_2 <95% at rest while breathing air as well as for individuals who are being considered for referral to the intensive care unit (ICU).

Table 1 Grading of severity of PCP based on measures of hypoxia

	Mild-to-moderate PCP	Moderate-to-severe PCP
Symptoms and signs	Increasing exertional breathlessness; with or without cough and sweats	Breathlessness on minimal exertion or at rest, persistent fever; with or without cough and sweats
Blood gas tensions (room air)	PaO_2 >9.3 kPa, $DA–aO_2$ ≤4.7 kPa	PaO_2 ≤9.3 kPa $DA–aO_2$ >4.7 kPa
SaO_2 (room air)	>92% at rest OR Falling on exercise by <3%	≤92% at rest OR Falling on exercise by ≥3%
Chest radiograph	Normal or minor diffuse interstitial shadowing	Moderate or extensive interstitial shadowing, with or without diffuse alveolar shadowing

$DA–aO_2$, alveolar to arterial oxygen tension gradient, calculated from blood gas analysis (as alveolar to arterial partial pressure oxygen gradient); PaO_2, partial pressure of oxygen; SaO_2, arterial oxygen saturation, measured with a transcutaneous oximeter; PAO_2 is estimated as $PIO_2 – PaCO_2/0.8$ (where PIO_2 is inspired oxygen tension at sea level breathing air i.e. 20 kPa and $PaCO_2$ is partial pressure of carbon dioxide). Signs and symptoms plus radiological features associated with differing severities are highlighted in the text.

5.3.4 Blood tests

Recommendation

- **We recommend measurement of serum (1-3)-β-D-glucan for people with suspected PCP (Grade 1B).**

Elevated serum lactic dehydrogenase (LDH) levels, reflecting lung injury, occur frequently but not universally in PCP [16]. Measurement of LDH has limited diagnostic value as elevated levels are not specific to PCP [7,14].

Measurement of serum (1-3)-β-D-glucan (BDG), a polysaccharide found in the cell wall of many fungi, is used increasingly as a diagnostic tool for PCP. Serum BDG levels are significantly higher in people with PCP, compared to those with a fungal pneumonitis due to aspergillosis or histoplasmosis, whereas non-fungal pneumonias do not usually cause elevations of BDG [17]. A positive serum BDG is suggestive of PCP when interpreted in the context of a compatible presentation with pneumonitis and consistent imaging findings but should be confirmed with a positive result from a specific *Pneumocystis*-specific assay (e.g. histochemical or molecular detection by PCR in BAL fluid or induced sputum; see below).

A systematic review and meta-analysis of the use of BDG for diagnosis of PCP in people living with HIV and those without HIV (who had other causes of immunosuppression) showed that the sensitivity among people living with HIV was 94% (95% confidence interval [CI] 91–96%) and the specificity was 83% (95% CI 69–92%). Among those with other causes of immunosuppression the sensitivity was 86% (95% CI 78–91%), and the specificity was 83% (95% CI 72–90%). A negative BDG result was only associated with a low post-test probability of PCP (5%) when the pre-test probability was low to intermediate (50%). Among individuals with a higher likelihood of PCP, the pooled sensitivity of BDG is insufficient to exclude infection. Based on these findings, a negative BDG result by itself does not 'rule out' a diagnosis of PCP in people living with HIV who have respiratory symptoms and are regarded as having a significant clinical risk of PCP [18]. Measuring BDG in BAL fluid has a poor positive-predictive value for the diagnosis of PCP, as oropharyngeal and upper respiratory tract colonisation with *Candida,* common in people at risk of PCP, may also give a positive result.

5.3.5 Respiratory sampling

As *Pneumocystis* is rarely identified in spontaneously expectorated sputum [7,14], this type of sample should not be used to diagnose or exclude PCP. Microscopy of induced sputum, generated by inhalation of aerosolised hypertonic saline, has a moderate-to-high diagnostic yield, ranging from <50% to >90% [7,14]. People with clinically suspected PCP and a negative result from sputum induction for *Pneumocystis* should be referred for bronchoscopy and BAL.

Fibre optic bronchoscopy with BAL has a diagnostic yield of >90% for diagnosis of PCP. The diagnostic yield is increased if multiple lobes are sampled, or the procedure is performed at the sites of greatest chest radiographic abnormality [14].

Detection of *Pneumocystis* using immunofluorescence (fluorescent, dye-labelled monoclonal antibodies) is more sensitive than using histochemical staining. However, immunofluorescence is expensive and accurate interpretation is dependent on the training of laboratory staff.

5.3.6 DNA amplification

Amplification of *Pneumocystis* DNA by PCR has high sensitivity for *Pneumocystis* detection in induced sputum and BAL fluid, with a sensitivity of 97–99% and specificity of 90–94% [19,20] for PCP. It is now the investigation of choice where available. A negative result is likely to

exclude PCP (negative predictive value ≥99%). The utility of molecular detection techniques is limited as *Pneumocystis* DNA may be found in respiratory samples from some immunodeficient patients who are colonised with *Pneumocystis*, including some without respiratory symptoms, and others who are symptomatic but who have a confirmed alternative diagnosis [21]. Additionally, although *Pneumocystis* DNA has been detected in spontaneously expectorated sputum, this has not been prospectively evaluated for diagnosis of PCP. Thus, while PCR may be replacing immunofluorescence in many clinical laboratories as the primary diagnostic test, results must be interpreted in the context of the clinical picture. Real-time (quantitative) PCR cycle threshold cannot currently be used to differentiate PCP from colonisation; however, detection of *Pneumocystis* DNA with a low cycle threshold value (i.e. a higher estimated *Pneumocystis* load) is strongly suggestive of PCP.

The detection of *P. jirovecii* by PCR in respiratory samples, in the absence of symptoms or signs of respiratory disease, should not *per se* trigger initiation of treatment for PCP. Treatment of suspected PCP should not be deferred in any individual pending results of sputum induction or bronchoscopy with lavage as significant clinical deterioration may occur. The diagnostic utility of conventional staining for *P. jirovecii* in BAL fluid from individuals with HIV is not impaired for up to 14 days after treatment is started [7,14]. However, the burden of detectable *Pneumocystis* DNA may fall rapidly in response to starting treatment [22,23].

5.3.7 Empirical treatment

Historically, in people living with HIV this approach was associated with higher mortality compared to treatment given for laboratory-confirmed PCP [24,25]. If empirical therapy is started it may adversely affect subsequent attempts to establish a laboratory-confirmed diagnosis of PCP if molecular diagnostic techniques are used, or to identify other pathogens that may have been missed and which have temporarily responded to trimethoprim-sulfamethoxazole (co-trimoxazole).

5.4 Clinical course of PCP

Assessment of the severity of PCP should be done at initial presentation using SaO_2 and arterial blood gas results (see Section 5.3.3). A PaO_2 of >9.3 kPa (while breathing room air) indicates mild-to-moderate PCP, and ≤9.3 kPa indicates moderate-to-severe disease; this approximately equates to SaO_2 >92% and ≤92% respectively. Using the alveolar–arterial

oxygen gradient, the severity of PCP can be classified as mild-to-moderate if ≤4.7 kPa or moderate-to-severe if >4.7 kPa (Table 1).

Untreated, moderate-to-severe PCP typically progresses to respiratory failure and death over several days. In the first few days of treatment, patients with PCP frequently experience a paradoxical deterioration in clinical status, with progression of infiltrates on chest radiography and reductions in oxygenation.

5.4.1 Prognostic factors

Several clinical and laboratory factors are associated with a poor outcome. These include, at clinical presentation: a patients' lack of knowledge of their HIV infection; older age; second (or subsequent) episode of PCP; poor oxygenation; marked chest radiographic abnormalities; peripheral blood leukocytosis; low haemoglobin or serum albumin levels; elevated serum LDH levels; and pregnancy. Other prognostic factors, identified subsequently, include: CMV or a bacterial or fungal co-pathogen in BAL fluid; elevated serum LDH enzyme levels that do not normalise despite treatment; pulmonary Kaposi's sarcoma; presence of extrapulmonary comorbidity; ICU admission; high Acute Physiology and Chronic Health Evaluation (APACHE) II score at ICU admission; need for assisted ventilation; and development of pneumothorax (whether breathing spontaneously or with assisted ventilation) [26-29].

5.5 Treatment of PCP

5.5.1 General measures

Supplemental oxygen given either via a tight-fitting facemask or using high-flow nasal oxygen should be given to hypoxaemic patients with PCP in order to maintain SaO_2 ≥90% or PaO_2 ≥8.0 kPa. If supplemental oxygen fails to maintain the SaO_2 or PaO_2 at these levels, respiratory support should be escalated. The patient should be assessed and transferred to the ICU, if appropriate, for consideration of non-invasive ventilation or endotracheal intubation and assisted ventilation with arterial blood gas monitoring through an arterial line [14,30].

5.5.2 First-line regimens for treatment of PCP

Recommendations

- **We recommend trimethoprim-sulfamethoxazole as the first-line treatment of choice for PCP of any severity (Grade 1A).**
- **We suggest that people who develop PCP despite taking trimethoprim-sulfamethoxazole as prophylaxis can be treated with standard high-dose trimethoprim-sulfamethoxazole (Grade 2C).**
- **We recommend that treatment should be continued in people living with HIV for 21 days (Grade 1B).**
- **We recommend that aerosolised pentamidine should not be used in the treatment of PCP because of its limited efficacy (Grade 1A).**

Patients with mild-to-moderate PCP may be treated with oral therapy as an outpatient with close clinical monitoring. Patients with moderate-to-severe PCP (i.e. PaO_2 <9.3 kPa at rest breathing room air) should receive intravenous therapy in hospital and can later be switched to oral therapy to complete treatment. Adjunctive corticosteroids are also given to those with moderate-to-severe PCP [31-34]. Benefit has been demonstrated only if corticosteroids are started within 72 hours of initiating specific anti-*Pneumocystis* therapy [31]. Trimethoprim-sulfamethoxazole is the treatment of choice for PCP of any severity [7,14,35,36] (Table 2).

Table 2 Treatment regimens for PCP

	Mild-to-moderate PCP	Moderate-to-severe PCP
First-choice regimen	Oral trimethoprim-sulfamethoxazole[a] (15–20 mg trimethoprim and 75–100 mg/kg/day sulfamethoxazole) in three divided doses, rounded to the nearest 480 mg tablet OR Oral trimethoprim-sulfamethoxazole: two double-strength (960 mg) tablets tds	Intravenous trimethoprim-sulfamethoxazole[a] (15–20 mg trimethoprim and 75–100 mg/kg/day sulfamethoxazole) in three or four divided doses[b,c]
Alternative regimens	Oral clindamycin 450 mg qds or 600 mg tds and oral primaquine[a] 30 mg[d] od OR Oral dapsone[a] 100 mg od and oral trimethoprim 15 mg/kg/day in three divided doses, rounded to the nearest 50 mg tablet OR Oral atovaquone 750 mg bd	Intravenous clindamycin 600 mg qds or 900 mg tds and oral primaquine[a] 30 mg[d] od OR Oral clindamycin 450 mg qds or 600 mg tds and oral primaquine[a] 30 mg[d] od OR Intravenous pentamidine isetionate 4 mg/kg od infused over 60 minutes

Adjunctive corticosteroids	No	Yes
Corticosteroid regimen	–	Start oral prednisolone (as soon as possible and within 72 hours of starting treatment for PCP) 40 mg bd: days 1–5 40 mg od: days 6–10 20 mg od: days 11–21 OR Intravenous methylprednisolone at 75% of the prednisolone dose (as above)

[a]Test for G6PD deficiency before starting trimethoprim-sulfamethoxazole, primaquine or dapsone, but do not delay the start of treatment. If G6PD deficiency is identified, or haemolysis occurs before G6PD deficiency is confirmed, change to an alternative treatment regimen; [b]can consider switching to oral administration when clinical improvement is observed; [c]treatment is often commenced with 20 mg trimethoprim/100 mg/kg sulfamethoxazole per day given on days 1–3, and reduced to 15 mg trimethoprim/75 mg/kg per day sulfamethoxazole starting on day 4 and continuing to day 21; [d]sometimes 15 mg primaquine is used.
od, once daily; bd, twice daily; tds, three times daily; qds, four times daily.

Mutations in the dihydropteroate synthase (*DHPS*) gene that confer sulfa resistance in other microorganisms have been described in *Pneumocystis* [37,38], but their clinical significance is unclear [38]. People who develop PCP despite taking trimethoprim-sulfamethoxazole as prophylaxis can be treated with standard high-dose trimethoprim-sulfamethoxazole. As with all anti-*Pneumocystis* drug regimens in people living with HIV, treatment should be continued for 21 days.

Adverse reactions to trimethoprim-sulfamethoxazole are common at these high doses and usually begin between 7 and 10 days of starting therapy and may require discontinuation of the drug in up to 50% of cases [7,14]. Common adverse drug reactions include fever, rash, cytopenias, hyperkalaemia and biochemical hepatitis. Most of these reactions appear to be caused by sulfamethoxazole, but the precise mechanisms are poorly understood. Trimethoprim competitively inhibits potassium excretion in the distal nephron in the same way as the potassium-sparing diuretic amiloride, and this is thought to be the cause of hyperkalaemia. Acute kidney injury and hyperkalaemia associated with trimethoprim-sulfamethoxazole are dose dependent [39].

Adverse effects from trimethoprim-sulfamethoxazole are not reduced in frequency or prevented by the use of N-acetyl cysteine or folinic acid. Additionally, folinic acid may reduce

the efficacy of trimethoprim-sulfamethoxazole [40], so should not be co-administered with trimethoprim-sulfamethoxazole.

Cutaneous reactions to trimethoprim-sulfamethoxazole range from a mild morbilliform rash to life-threatening 'skin failure' syndromes (e.g. toxic epidermal necrolysis or Stevens-Johnson syndrome). In some cases, rash and fever may resolve spontaneously, or respond to conservative measures including antihistamines; however, trimethoprim-sulfamethoxazole may need to be discontinued. Oral corticosteroids can be helpful. Caution is required if desensitisation is attempted in patients who have experienced cutaneous reactions to trimethoprim-sulfamethoxazole.

Several alternative regimens can be used for treatment of mild-to-moderate PCP (Table 2). A combination of trimethoprim with dapsone, both given orally, has been shown to be as effective as trimethoprim-sulfamethoxazole in patients with mild-to-moderate PCP, and is less toxic [35,41]. Major adverse reactions to dapsone include fever, nausea and vomiting, rash and methaemoglobinaemia. Haemolysis can rarely occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency after dapsone treatment, although this is not a contraindication to the use of dapsone in PCP as benefits are likely to outweigh risks significantly. Caution is advised in administering dapsone to patients who have experienced adverse reactions to sulfonamides or the HIV protease inhibitor darunavir, due to similarities in the sulfa moiety.

Several studies have shown that the combination of clindamycin and primaquine has comparable efficacy and toxicity to trimethoprim-sulfamethoxazole [35,42,43] and trimethoprim with dapsone [35] in the treatment of mild-to-moderate PCP. Treatment may also be initiated with intravenous clindamycin in those with moderate-to-severe PCP, and then administered orally following clinical recovery. Adverse drug reactions to primaquine are less common when 15 mg, rather than 30 mg, once daily is used and include diarrhoea, fever, methaemoglobinaemia, neutropenia and rash.

Atovaquone is less effective than trimethoprim-sulfamethoxazole and shows equivalent efficacy to intravenous pentamidine in the treatment of mild-to-moderate PCP, but it is better tolerated [36,44]. Adverse reactions to atovaquone include fever, gastrointestinal symptoms, abnormal liver function tests and rash.

For moderate-to-severe PCP, based on a retrospective study and a systematic review, the combination of clindamycin and primaquine is the preferred alternative regimen to trimethoprim-sulfamethoxazole. The combination of clindamycin and primaquine was

shown to be superior to pentamidine as 'salvage' treatment of PCP in patients not responding to first-line treatment [45,46]. *Clostridioides difficile* infections are particularly associated with the use of clindamycin, and clinicians should be alert to the development of diarrhoea in patients receiving the drug.

Intravenous pentamidine is almost as effective as trimethoprim-sulfamethoxazole for the treatment of PCP but is less often used due to significant toxicity [45,47]. Adverse effects from intravenous pentamidine include acute kidney injury, cardiac arrhythmias (e.g. torsades de pointes and ventricular tachycardia), hypotension, pancreatitis, hypoglycaemia and hyperglycaemia, hyperkalaemia, hypomagnesaemia and hypocalcaemia. The mechanism of pentamidine-induced hyperkalaemia is similar to that caused by trimethoprim. Acute kidney injury and hypoglycaemia are associated with high serum pentamidine levels, duration of treatment and cumulative drug dose.

Aerosolised pentamidine has no role in the treatment of PCP because of its limited efficacy [48,49].

Caspofungin is an effective treatment for *Aspergillus* and *Candida* infections. Several case series and additional retrospective observational studies have shown that caspofungin may be effective as salvage therapy either as monotherapy or in combination with other agents in patients with PCP who are not responding to, or who are intolerant of, first-line therapy [50]. There have been no prospective evaluations of caspofungin monotherapy compared to trimethoprim-sulfamethoxazole, clindamycin with primaquine, or other regimens as first-line therapy for PCP.

5.5.3 Adjunctive corticosteroids

Recommendation

- **We recommend that patients with laboratory proven or clinically suspected PCP and PaO_2 <9.3 kPa, or SaO_2 ≤92% at rest or falling by ≥3% on exercise, should receive adjunctive corticosteroids as soon as is possible and within 72 hours of starting anti-*Pneumocystis* treatment for maximal benefit (Grade 1A).**

Several studies have shown that administration of corticosteroids during the first 72 hours of treatment of HIV-associated PCP can prevent or reduce the decline in oxygenation that is observed in some patients, as well as improving survival [31]. Adjunctive corticosteroids are widely used by clinicians. A systematic review and a more recent meta-analysis support the

use of corticosteroids both in reducing mortality and in the need for assisted ventilation [32,33]. Patients with laboratory proven or clinically suspected PCP and PaO_2 <9.3 kPa, or SaO_2 ≤92% at rest or falling by ≥3% on exercise, should receive adjunctive corticosteroids as soon as is possible and within 72 hours of starting anti-*Pneumocystis* treatment for maximal benefit.

5.5.4 Management of treatment failure

Recommendations

- **We suggest waiting at least 4 days before switching therapy in the absence of clinical improvement (Grade 2C).**
- **We suggest switching therapy for individuals who develop toxicity related to trimethoprim-sulfamethoxazole. Those with moderate-to-severe and mild-to-moderate PCP can be given oral primaquine combined with intravenous or oral clindamycin; those with mild disease can be given atovaquone (Grade 2B).**

Treatment failure is defined as a lack of improvement or worsening of oxygenation with/without worsening of chest radiographic appearances between days 4 and 8 of anti-*Pneumocystis* treatment. Failure attributed to treatment occurs in approximately 10% of patients with mild-to-moderate PCP [45,46]. There are no robust clinical data on the best management of PCP treatment failure to inform clinicians.

Clinicians should wait at least 4 days before switching therapy because of a lack of clinical improvement. An early and reversible clinical deterioration frequently occurs within the first 3 to 5 days of PCP treatment, as discussed in Section 5.4, and is probably a result of the inflammatory response caused by antimicrobial-induced killing of *Pneumocystis* organisms in the lung.

Concomitant infection(s), fluid overload, methaemoglobinaemia and pneumothorax must be excluded as possible causes of clinical deterioration before treatment is changed [14]. Additionally, bronchoscopy (with BAL) should be performed if PCP treatment is being given empirically. Having excluded other causes, any patient not responding between 4 and 8 days should be switched to alternative therapy as shown in Table 2.

Treatment failure resulting from treatment-limiting toxicity occurs in more than a quarter of patients. Switching to another regimen is the best management for treatment-related toxicity [45,46] (see Table 2).

5.6 When should ART be started when treating PCP?

Recommendation

- **We recommend that ART should be initiated, when possible, within 2 weeks of diagnosis of PCP (Grade 1B).**

When possible, ART should be initiated within 2 weeks of PCP diagnosis [51,52]. Some clinicians prefer to defer starting ART in patients in the ICU until they no longer require assisted ventilation, given the small risk of ART-induced immune reconstitution inflammatory syndrome (IRIS) provoking a rapid deterioration in respiratory function.

5.7 IRIS

IRIS following an episode of PCP is rare and mostly occurs within weeks of the episode. Manifestations include fever and recurrence or worsening of cough and shortness of breath, as well as worsening of previously improving chest radiographic appearance, thus mimicking a relapse of PCP. Management of PCP-associated IRIS is not well defined; some clinicians recommend use of corticosteroids in this setting if other causes have been excluded.

5.8 Prophylaxis for PCP

5.8.1 Infection control: reducing exposure to *Pneumocystis*

Accumulating evidence demonstrates that *Pneumocystis* is transmissible in experimental animal models and in humans [7]. *P. jirovecii* has been detected in the air near hospitalised people with PCP [53] and many outbreaks of PCP, each associated with specific genotypes of *P. jirovecii,* have been reported in kidney transplant units [54,55]. These data suggest that isolating individuals with PCP within healthcare settings from people at risk of PCP might prevent nosocomial transmission, however currently this is not always done and the evidence base to support isolation is incomplete. It may be prudent to isolate any person living with HIV who is hospitalised for investigation and treatment of respiratory symptoms, at least until TB has been excluded.

5.8.2 Preventing a first episode of PCP (primary prophylaxis)

Recommendations

- **We recommend that all adults living with HIV with a CD4 count <200 cells/mm^3 should receive prophylaxis to prevent PCP (Grade 1A).**

- **We suggest that individuals who have a CD4 percentage of total lymphocytes <14% should be offered PCP prophylaxis (Grade 2B).**
- **We suggest that primary prophylaxis could be started in individuals with CD4 counts between 200 and 250 cells/mm^3 if ART is delayed or 3-monthly monitoring of CD4 count is not possible (Grade 2B).**
- **We recommend that prophylaxis to prevent PCP is not needed for individuals receiving sulfadiazine with pyrimethamine for treatment or secondary prevention of cerebral toxoplasmosis (Grade 1B).**
- **We recommend trimethoprim-sulfamethoxazole 960 mg (one double-strength tablet) or 480 mg (one single-strength tablet) once daily to prevent a first episode of PCP (Grade 1A).**
- **We recommend trimethoprim-sulfamethoxazole 960 mg three times a week as an alternative regimen to prevent a first episode of PCP (Grade 1B).**

All adults living with HIV, including those who are taking ART and women who are pregnant, who have CD4 counts <200 cells/mm^3 should receive prophylaxis to prevent a first episode of PCP [56,57]. Individuals who have a CD4 percentage of total lymphocytes <14% should also be offered prophylaxis to prevent PCP [56,57].

After diagnosis of HIV if initiation of ART is delayed for any reason or monitoring of CD4 count every 3 months is not possible, primary prophylaxis could be started in individuals with CD4 counts between 200 and 250 cells/mm^3 [56]. Individuals receiving sulfadiazine with pyrimethamine for treatment or secondary prevention of cerebral toxoplasmosis do not additionally need prophylaxis to prevent PCP [58].

The recommended regimen of choice for preventing a first episode of PCP is trimethoprim-sulfamethoxazole one double-strength (960 mg) tablet once daily [59-61] (Table 3). One single-strength trimethoprim-sulfamethoxazole tablet (480 mg) once daily is better tolerated and appears to also be effective in preventing PCP [61]. As there is strong evidence to support both regimens but they have not been directly compared, a clinician might consider using single-strength trimethoprim-sulfamethoxazole once daily because it is associated with better tolerability and fewer side effects. Trimethoprim-sulfamethoxazole 960 mg three times a week also provides protection against a first episode of PCP [62]. One double-strength trimethoprim-sulfamethoxazole tablet daily additionally provides cross-protection against development of cerebral toxoplasmosis [63], as well as many (respiratory) bacterial

infections [58], while one single-strength tablet also appears effective at preventing *Toxoplasma* encephalitis [64].

Table 3 Primary and secondary prophylaxis for PCP

When to start primary prophylaxis: CD4 count <200 cells/mm^3 OR CD4 percentage <14% of total lymphocytes OR CD4 count between 200 and 250 cells/mm^3 if initiation of ART is delayed and if regular CD4 count monitoring is not possible
When to start secondary prophylaxis: After a previous episode of PCP
Regimens for primary and secondary prophylaxis: *First-choice regimen* Trimethoprim-sulfamethoxazole one double-strength tablet (960 mg) od OR Trimethoprim-sulfamethoxazole one single-strength tablet (480 mg) od *Alternative regimens* Trimethoprim-sulfamethoxazole one double-strength tablet (960 mg) three times per week OR Dapsone 100 mg od or 50 mg bd OR Dapsone 50 mg od plus pyrimethamine 50 mg and folinic acid 25 mg, both once a week OR Dapsone 200 mg plus pyrimethamine 75 mg and folinic acid 25 mg, all once a week OR Nebulised pentamidine 300 mg, given via a Respirgard II® nebuliser, once a month[a] OR Atovaquone 1500 mg od with food OR Atovaquone 1500 mg od with food, plus pyrimethamine 25 mg and folinic acid 10 mg od
Primary and secondary prophylaxis can be discontinued: After starting ART when CD4 count has increased from <200 to ≥200 cells/mm^3 for ≥3 months After starting ART when CD4 count is between 100 and 200 cells/mm^3, and the plasma HIV viral load remains undetectable (<50 copies/mL) for ≥3 months
Primary and secondary prophylaxis should be restarted if: CD4 count is <100 cells/mm^3, irrespective of plasma HIV viral load CD4 count is between 100 and 200 cells/mm^3 and there is a detectable HIV viral load (≥50 copies/mL)

[a]Nebulised pentamidine 300 mg every 2 weeks can be considered in individuals with a CD4 count <50 cells/mm^3, or a previous episode of PCP and still requiring preventive therapy.
od, once daily; bd, twice daily.

5.8.3 Managing toxicity

Recommendations

- **We recommend that individuals who experience minor adverse reactions when taking trimethoprim-sulfamethoxazole as prophylaxis should continue trimethoprim-sulfamethoxazole if possible, with supportive care before discontinuation (Grade 1C).**
- **We recommend that if prophylaxis is discontinued because of a mild adverse reaction, restarting trimethoprim-sulfamethoxazole should be considered once the individual has recovered (Grade 1B).**
- **We suggest that trimethoprim-sulfamethoxazole may be restarted by gradually increasing the dose, which is known as 'desensitisation' (Grade 2A).**
- **We recommend that trimethoprim-sulfamethoxazole should be stopped in individuals with life-threatening reactions and not restarted (Grade 1C).**

Individuals taking trimethoprim-sulfamethoxazole (as prophylaxis) who experience minor adverse reactions, including fever and rash, should continue trimethoprim-sulfamethoxazole if possible. Supportive care for common adverse effects should be attempted before trimethoprim-sulfamethoxazole is discontinued. If prophylaxis is discontinued because of a mild adverse reaction, restarting trimethoprim-sulfamethoxazole should be considered once the individual has recovered from the reaction. Alternatively, trimethoprim-sulfamethoxazole may be restarted by gradually increasing the dose ('desensitisation') (Table 4). In individuals with life-threatening reactions due to trimethoprim-sulfamethoxazole, including toxic epidermal necrolysis or Stevens-Johnson syndrome, trimethoprim-sulfamethoxazole should be stopped and further exposure should be avoided.

Table 4 Protocol for trimethoprim-sulfamethoxazole desensitisation among adults and adolescents

	Dose
Day 1	16 mg trimethoprim + 80 mg sulfamethoxazole (oral suspension[a])
Day 2	32 mg trimethoprim + 160 mg sulfamethoxazole (oral suspension[a])
Day 3	48 mg trimethoprim + 240 mg sulfamethoxazole (oral suspension[a])
Day 4	64 mg trimethoprim + 320 mg sulfamethoxazole (oral suspension[a])
Day 5	One single-strength trimethoprim-sulfamethoxazole tablet (80 mg trimethoprim + 400 mg sulfamethoxazole)

Optional, if using trimethoprim-sulfamethoxazole 960 mg od as prophylaxis	
Day 6, and subsequently	Two single-strength trimethoprim-sulfamethoxazole tablets OR One double-strength trimethoprim-sulfamethoxazole tablet (160 mg trimethoprim + 800 mg sulfamethoxazole)

[a] Oral suspension is available at varying strengths, including 240 mg/5 ml and 480 mg/5 ml, therefore adjust volume administered to required concentration.
od, once daily.

5.8.4 Alterative regimens for primary and secondary prophylaxis

Recommendation

- **For individuals who cannot tolerate trimethoprim-sulfamethoxazole, we suggest nebulised pentamidine, dapsone, dapsone and pyrimethamine with folinic acid, or atovaquone (Grade 2A).**

Alternative regimens are available for individuals who cannot tolerate trimethoprim-sulfamethoxazole (Table 3). These include nebulised pentamidine given via a Respirgard II® nebuliser (or an equivalent delivery system generating appropriately sized droplets) [59], dapsone [60], dapsone and pyrimethamine with folinic acid [63,65] or atovaquone [66,67]. Nebulised pentamidine, dapsone and atovaquone are equally effective, however atovaquone is more expensive [66,67]. Nebulised pentamidine should not be used as prophylaxis in individuals unable to tolerate trimethoprim-sulfamethoxazole who have *Toxoplasma* immunoglobulin G antibodies as it does not provide prophylaxis against *Toxoplasma* encephalitis.

There are insufficient data to support the use of oral clindamycin with primaquine or intravenous pentamidine given once a month or every 2 weeks as alternatives to trimethoprim-sulfamethoxazole. There are limited data on the use of nebulised pentamidine delivered via a nebuliser system other than Respirgard II®.

5.8.5 When can primary prophylaxis for PCP be stopped?

Recommendations

- **We recommend that primary prophylaxis can be discontinued in individuals who have responded to ART with an increase in CD4 count to >200 cells/mm^3 for >3 months (Grade 1A).**

- **We recommend that primary prophylaxis can be stopped in individuals with CD4 counts between 100 and 200 cells/mm^3 if the plasma HIV load remains undetectable for 3–6 months (Grade 1B).**

Primary prophylaxis can be discontinued in individuals who have responded to ART with an increase in CD4 count to >200 cells/mm^3 for >3 months [68-72]. Additionally, there is evidence to support stopping primary prophylaxis in individuals with CD4 counts between 100 and 200 cells/mm^3 if the plasma HIV load remains undetectable (<50 copies/mL) for 3 to 6 months [73-75] (Table 3).

5.8.6 Preventing recurrence of PCP (secondary prophylaxis)

Recommendation

- **We recommend that secondary prophylaxis with trimethoprim-sulfamethoxazole should be started immediately after completing treatment for PCP and continued until immune reconstitution occurs in response to commencing ART (Grade 1A).**

Secondary prophylaxis with trimethoprim-sulfamethoxazole should be started immediately after completing treatment for PCP. Trimethoprim-sulfamethoxazole should be continued until immune reconstitution (Table 3) occurs in response to commencing ART. Alternative regimens for individuals who are unable to take trimethoprim-sulfamethoxazole are: nebulised pentamidine given via a Respirgard II® nebuliser; dapsone; dapsone and pyrimethamine with folinic acid; or atovaquone (Table 3).

5.8.7 When can secondary prophylaxis be stopped?

Secondary prophylaxis can be discontinued in individuals whose CD4 count has increased to >200 cells/mm^3 for >3 months as a result of starting ART [69]. Based on results from the COHERE study, secondary prophylaxis can be stopped in individuals with CD4 counts >100 cells/mm^3 in whom plasma HIV levels remain undetectable for 3–6 months [76] (Table 3).

5.8.8 When should primary or secondary prophylaxis be restarted?

Primary and secondary prophylaxis should be restarted if an individual's CD4 count decreases to <100 cells/mm^3, irrespective of the plasma HIV load. Prophylaxis should also be restarted in individuals with a detectable plasma viral load and CD4 counts of 100–200 cells/mm^3 (Table 3).

5.9 PCP in pregnancy

The presentation and diagnosis of PCP in pregnancy is the same as in women who are not pregnant. Some studies have shown an increased mortality from PCP in pregnancy, however data are limited [77].

The treatment of PCP in pregnancy is discussed in a separate chapter of the opportunistic infection guidelines [78].

6 Bacterial pneumonia

6.1 Background and epidemiology of bacterial pneumonia

Recommendations

- **We recommend that pneumonia should be considered a possible indicator of HIV infection and an opportunity for HIV testing in line with testing guidelines [79] (Grade 1C).**
- **Gram-negative pathogens should be considered especially likely in people living with HIV who develop pneumonia when hospitalised (GPP).**

Bacterial infection of the lower respiratory tract is common in people living with HIV [80,81]. Dysfunctional innate and adaptive immune responses appear to be important and pneumonia can occur at all levels of immunosuppression [82-84]. A number of long-term patient cohorts have demonstrated declining rates of pneumonia with use of ART but rates remain elevated compared to populations without HIV [85-88]. Risk factors for bacterial pneumonia in people living with HIV are detectable viral load (including due to treatment interruptions), low nadir CD4 cell count, incomplete immune reconstitution on ART (<500 cells/mm^3) and declining CD4 cell counts, as well as impaired renal function, injecting drug use and cigarette smoking [80,89-92]. Because of increasing longevity of people living with HIV in addition to high numbers of current and former smokers, COPD is an increasingly important risk factor for pneumonia [93,94]. An episode of pneumonia should be considered a possible indicator event for HIV infection and thus an opportunity for HIV testing [95]. Recurrent pneumonia (two or more episodes in a 12-month period) is classified as AIDS defining [96].

The aetiology of bacterial pneumonia among people living with HIV is similar to that among people without HIV. *Streptococcus pneumoniae* is consistently the most commonly found organism [97-101]. Other common organisms include *Haemophilus influenza, Staphylococcus aureus, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [82,98, 102-104]. Microbiome studies have suggested that people living with HIV may tend to a skewed bacterial community with an increase in gram-negative organisms and *Pseudomonas* spp. [105]. However, infections due to *P. aeruginosa*, which are associated with very low CD4 counts or structural lung disease, have decreased with greater access to ART and are now less common [99]. 'Atypical' organisms such as *Legionella pneumophila, Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have not been frequently reported in HIV-related bacterial pneumonia, although this may reflect diagnostic difficulties and frequencies may be similar to in people without HIV [106-108]. As with people without HIV, gram-negative pathogens should be considered especially likely in those who develop pneumonia when hospitalised. Rare organisms such as *Rhodococcus equi* and *Nocardia* spp. have been reported in association with HIV and should be considered in non-resolving cases and/or in people who are severely immuncompromised (e.g. CD4 count <50 cells/mm^3) [109,110].

6.2 Presentation of bacterial pneumonia

Recommendation

- **For people requiring hospitalisation, a blood culture should be obtained before starting antimicrobials and urine antigen testing for *Pneumococcus* and *Legionella* should be performed (GPP).**

The presenting symptoms of bacterial pneumonia in people living with HIV are similar to those in people without HIV [98,111-113]. Symptoms include fever, cough, pleuritic chest pain and breathlessness and typically have an acute onset (hours to days). The physical signs are those of lung consolidation, and possibly pleural effusion in more complicated cases. Although clinical severity scores such as the Pneumonia Severity Index (PSI) and CURB-65 have not been prospectively evaluated in people living with HIV, retrospective studies have shown them to have utility in guiding management, including the need for hospitalisation and intensive care [114,115]. The peripheral blood white cell count is usually elevated with a neutrophilia but may be low in more severe cases. Elevations of C-reactive protein and procalcitonin are sensitive for bacterial pneumonia but without sufficient specificity in practice to reliably differentiate bacterial pneumonia from other causes such as TB, PCP,

SARS-CoV-2 or influenza [116-120]. In suspected pneumonia, a chest radiograph should be obtained in all hospitalised patients and in outpatients in whom the diagnosis is in doubt, who are thought to have an underlying lung pathology or who are not responding to therapy. Radiological features are similar to those in people without HIV and the absence of consolidation should prompt a re-evaluation of the diagnosis [100,101]. CT scans of the thorax may help if the diagnosis is uncertain (PCP, TB and cryptococcal pneumonia can also present acutely) or if additional pathology could be present (such as lung cancer).

Microbiological testing should be attempted as this can help to guide treatment decisions. Where possible a spontaneous sputum sample for Gram staining and culture should be obtained prior to antimicrobial therapy. Lower respiratory tract samples can be tested by nucleic acid amplification for a panel of viral and bacterial causes of pneumonia including influenza, SARS CoV-2 and 'atypical' bacterial pathogens [121]. In cases requiring hospitalisation, a blood culture should also be obtained (much higher rates of bacteraemia were reported in people living with HIV compared to people without HIV in the era before widespread ART) and urine antigen testing for *Pneumococcus* and *Legionella* should be performed [101,122]. In uncomplicated cases, further lung sampling either by sputum induction or bronchoscopy with BAL should be considered in those who are not responding (usually after a CT scan to guide sampling). If pleural fluid is detected, sampling via ultrasound should be considered.

6.3 Treatment of bacterial pneumonia

Recommendation

- **We recommend that people living with HIV with community-acquired bacterial pneumonia should be treated in the same way as people without HIV and as outlined in community-acquired pneumonia guidelines (Grade 1D).**

National guidelines for the management of community-acquired pneumonia have been published and these should be used in treating people living with HIV [123-125]. Local guidance is also available in Scotland [126] and local Microguide in England (e.g. see [127] for Lewisham and Greenwich NHS Trust). Initial anti-microbial treatment is usually empirical and should be chosen according to: (i) pneumonia severity; (ii) the likelihood of particular pathogens as indicated by risk factors; (iii) the potential for antimicrobial resistance; (iv) potential toxicities; and (v) local antimicrobial recommendations. Decisions concerning outpatient versus hospital treatment, oral or intravenous antimicrobials and treatment

duration should be made based on assessment of severity and other comorbidities likely to affect outcome [123,124]. Treatment should be modified according to microbiological results when available. In non-responding cases, treatment should be altered in discussion with clinical microbiology experts taking into account local epidemiology.

6.4 Follow-up of bacterial pneumonia

Recommendation

- **We suggest that people living with HIV with bacterial pneumonia should have a follow-up chest radiograph if clinical features have not resolved, they are aged over 50 or are smokers (Grade 2C).**

Routine follow-up by chest X-ray is usually performed in all cases of moderate-to-severe pneumonia but its utility is debated. All patients with persistent signs or symptoms or at increased risk of malignancy (e.g. aged over 50 years or smokers) should be followed up to ensure clinical and radiological resolution [123]. This is particularly important in individuals at increased risk of underlying lung cancer. Follow-up should include discussion of smoking cessation and vaccination.

6.5 Prophylaxis for bacterial pneumonia

Recommendations

- **We recommend that people living with HIV should be offered pneumococcal vaccination according to national guidelines (Grade 1C).**
- **We recommend that people living with HIV who have bacterial pneumonia and are current smokers should be offered a smoking cessation intervention (Grade 1C).**

A single dose of pneumococcal polysaccharide vaccine (PPV) is recommended by the UK Health Security Agency for all individuals over the age of 65 years; vaccination is also recommended for people between 18 and 64 years old living with HIV as they are deemed to be in a 'high-risk' group for pneumococcal infection [128]. Pneumococcal and haemophilus vaccination strategies are discussed in the BHIVA immunisation guidelines [6]. People living with HIV should receive a single dose of pneumococcal conjugate vaccine (PCV)13 and anyone eligible for PPV23 should receive it through the national programme at least 3 months after PCV13 [6,128]. The safety and efficacy of pneumococcal vaccination have been demonstrated in people living with HIV [129].

Smoking cessation is a crucial part of pneumonia prevention [130]. Smoking status should be discussed with all individuals and the opportunity taken to offer brief smoking cessation interventions, by appropriately trained staff who can arrange more formal interventions, when needed [131,132].

6.6 Starting ART after an episode of bacterial pneumonia

Recommendation

- **We recommend that ART should be started within 2 weeks of initiating pneumonia therapy in those not already on ART (Grade 1B).**

Individuals with bacterial pneumonia who are not already on ART, should be started on ART within 2 weeks of initiating therapy for pneumonia [52].

7 Influenza

7.1 Epidemiology and presentation of influenza

People living with HIV should receive ART to reduce the risk of infection, hospitalisation and death from influenza. Presentation of influenza is similar in people living with HIV compared to other patient groups. Cough, fever, pharyngitis and myalgia are the most common symptoms, while dyspnoea, rhinorrhoea, headache and gastrointestinal upset are less common, as evidenced by the presentation of pandemic H1N1 (pH1N1) in a range of countries [133]. However, studies from the pre-ART era suggested a 2-fold increase in attack rate for seasonal influenza A and a 2- to 5-fold greater risk of developing more severe disease in people living with HIV [134,135]. This outcome was independent of CD4 count or viral load suggesting a major role for concomitant medical comorbidities [136] or smoking [134]. However, excess deaths attributable to seasonal influenza A have been estimated to be many-fold greater among people living with advanced HIV disease compared to the general population [137] and observational epidemiological studies both prior to and during the 2009 pandemic showed an increased incidence of influenza A complications in people living with HIV not on ART [134,135,138,139].

With the advent of the ART era there has been a reduction in mortality in those hospitalised with influenza A [140]. Studies conducted where ART coverage was high at the time of the H1N1 pandemic demonstrated that the incidence, presentation and severity of pH1N1 influenza A were broadly similar in people with and without HIV [138,141,142]. However, in low- and middle-income countries where ART availability may be more limited,

HIV-seropositive individuals had a 4- to 8-fold higher risk of hospitalisation and a 20-fold higher risk of death from pandemic or seasonal influenza A between 2009 and 2013 [143-145]; these risks were further increased if individuals were also diagnosed with AIDS [137]. Direct comparisons among people living with HIV hospitalised with pH1N1 suggest that being on ART is associated with shorter hospital stays, reduced likelihood of mechanical ventilation and potentially reduced mortality [138,139]. However, a population case–control study in South Africa that covered pH1N1 and seasonal influenza A periods found that people living with HIV hospitalised with influenza A were more likely to be on ART than the general HIV population [146]. This may have been confounded by under-reporting of ART use in the general HIV population.

7.2 Diagnosis of influenza

Recommendation

- **Influenza and COVID-19 tests should be performed in people living with HIV with an influenza-like syndrome, pneumonia or exacerbation of a chronic respiratory syndrome (e.g. asthma or COPD) during periods when influenza is circulating, unless national guidance during pandemics suggests an alternative strategy for the general population (GPP).**

In suspected cases, diagnosis of influenza is confirmed by detection of viral RNA from nasopharyngeal or nasal swabs. Testing is now most often accomplished by a rapid viral nucleic acid amplification test (a rapid molecular test) with a sensitivity of 91% and specificity of 96% on meta-analysis [147]. Rapid influenza diagnostic tests that assess for the presence of antigen may be cheaper, but have lower detection rates and are not able to distinguish influenza A virus subtypes so real-time PCR will further enhance diagnosis in hospitalised patients [148].

7.3 Treatment of influenza

Recommendations

- **We suggest that people living with HIV should be treated when influenza is detected and can start treatment within 48 hours of symptom onset (Grade 2D).**
- **We suggest that people living with HIV should receive the NI oseltamivir (assuming that the majority of circulating strains in a given influenza season show susceptibility) (Grade 2D).**

- **We suggest that for individuals with significant immunosuppression (CD4 count <200 cells/mm^3), treatment may be administered if afebrile or if symptoms have been present for more than 48 hours (Grade 2D).**
- **We suggest that when people living with HIV continue to shed virus or show no symptomatic improvement 7–10 days after initiation of antivirals for influenza A, therapy should be switched to an alternative antiviral based on current predicted sensitivity with testing of the strain for NI resistance if available (Grade 2D)**.

There have been no prospective controlled trials of NI treatment in people living with HIV. These recommendations are based on National Institute for Health and Care Excellence (NICE) guidance recommending that NIs are used to treat 'at risk' individuals when influenza A is detected, or individuals who present with an influenza-like illness at a time when national surveillance schemes indicate that influenza A or B is circulating, and treatment can be started within 48 hours of symptom onset [149]. The recommendation to treat 'at risk' groups, which include 'people who might be immunosuppressed', is based on greater quality-adjusted life-year gains in this group from reductions in time to alleviation of symptoms and return to normal activity in randomised placebo-controlled trials of NIs but with no increase in overall, serious or drug-related adverse effects [149].

Evidence from observational studies indicated a reduced risk of severe disease and death in people with HIV with pH1N1 treated with NIs, particularly if treatment was not delayed [139,150-152].

Oseltamivir 75 mg twice daily given orally for 5 days is currently the preferred NI [153,154]. Inhaled zanamivir 10 mg (two puffs) twice daily via an inhalation device for 5 days is an alternative NI [155]. For critically ill individuals, peramivir is a parenterally formulated NI that is licensed in the UK, but there are no data on its use in people living with HIV.
Most pH1N1 influenza A virus strains in 2009–2010 retained susceptibility to NIs, but emergence and selection of strains with reduced susceptibility to oseltamivir during antiviral therapy have been reported in individuals living with HIV [156,157]. In addition, seasonal influenza A virus strains in 2008–2009 were frequently resistant to oseltamivir, and resistant strains have been detected in individuals with no previous oseltamivir exposure in subsequent influenza seasons [158,159]. These strains remained susceptible to zanamivir thus the selection of the most appropriate NI must be made considering the prevailing susceptibility of the strain(s) circulating in a given influenza season in consultation with local

virologists. However, multi-resistant strains have been reported in other immunocompromised groups [160,161].

Baloxavir marboxil is an endonuclease inhibitor that achieves similar reductions in time to symptom alleviating compared to NIs and is approved by the US Food and Drug Administration. NICE has been unable to make a recommendation on baloxavir marboxil for the treatment of influenza [162]. There are no data on its use in people living with HIV.

There are no data to support better outcomes or reduced resistance with combination treatment (an NI plus baloxavir marboxil) compared to an NI alone in the general population or in people living with HIV [163].

7.4 Prophylaxis for influenza

Strategies for influenza vaccination in people living with HIV are discussed in the BHIVA immunisation guidelines [6]. The recommendation below is based on these strategies.

Recommendation

- **We recommend that people living with HIV should be offered annual influenza vaccination with a parenteral non-replicating vaccine, and this includes pregnant women living with HIV (Grade 1A) as per the BHIVA immunisation guidelines.**

8 Cryptococcosis

8.1 Epidemiology of cryptococcal disease

Pulmonary infection results from inhalation of *Cryptococcus* spp. and is usually due to *C. neoformans* which is found worldwide, though *C. gatii* may cause infection in Northern Australia and the Pacific Northwest region of North America.
Symptomatic pulmonary cryptococcosis in people living with HIV is typically a disease associated with CD4 counts <100 cells/mm^3, and widespread use of ART has dramatically reduced the incidence of all cryptococcal infection in people living with HIV [164]. For further details, see the central nervous system (CNS) chapter of the BHIVA opportunistic infection guidelines [165].

8.2 Presentation of cryptococcal disease

8.2.1 Extensive pulmonary disease

HIV-associated pulmonary cryptococcosis in the era before combination ART was associated with a more acute presentation than pulmonary cryptococcosis observed in

other clinical settings [164]. The presenting symptoms are indistinguishable from those of PCP, with fever, cough (which may be productive), exertional dyspnoea and pleuritic chest pain often present [166,167]. Chest radiographs most often show interstitial infiltrates or sometimes areas of consolidation, although solitary or widespread nodules, cavities, intrathoracic lymphadenopathy or pleural effusions are also recognised in people living with HIV [166,168]. Diffuse interstitial infiltrates, which may contain small nodules or have a miliary appearance [169], are most common in individuals with advanced immunosuppression or those with co-infections [166,168]. As with PCP, pneumothoraces may develop [170].

8.2.2 Localised pulmonary disease

Disseminated disease is the most common presentation of cryptococcosis in people living with HIV (see the CNS chapter of the BHIVA opportunistic infection guidelines [165]) and localised pulmonary disease, which is often occult, is common in this setting. In a Chinese study in the era of ART, chest CT scanning was performed in people living with HIV with evidence of invasive cryptococcal infection, as determined by detection of cryptococcal antigen or isolation of cryptococci in the blood [171]. Approximately three-quarters of individuals had cryptococcal meningitis and most were either asymptomatic or reported a cough as their only respiratory syndrome. In this setting 93% of individuals had nodules on chest CT scans and these were most often solitary and associated with cavitation. This emphasises that focal pulmonary disease with cough may be the most frequent pulmonary form of cryptococcosis in people with HIV and invasive cryptococcal infection.

8.3 Diagnosis of cryptococcal disease

Recommendations

- **We recommend that pulmonary cryptococcosis should be diagnosed by culture or microscopic identification of yeast in a biopsy specimen or BAL or pleural fluid (Grade 1C).**
- **We recommend serum cryptococcal antigen testing for all individuals with suspected pulmonary cryptococcosis and if positive a lumbar puncture should be offered to exclude cryptococcal meningitis (Grade 1C).**

C. neoformans is identified in induced sputum or BAL or pleural fluid by Giemsa stain, India ink stain (which reveals an encapsulated yeast) or calcofluor white with fluorescence

microscopy. Mucicarmine also stains the capsule intensely and can be used. Cryptococcal antigen can be detected in BAL fluid (sensitivity 100% and specificity 98%) [172]. The yeast can be cultured from BAL or biopsy specimens using blood agar or fungal medium such as Sabouraud medium [166]. Diagnosis usually requires culture of the yeast with or without a positive antigen test or staining of yeast in 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 suggests disseminated disease. A serum cryptococcal antigen test should always be performed in people with HIV and pulmonary cryptococcus, and a positive serum cryptococcal antigen or blood culture result should trigger cerebrospinal fluid (CSF) examination to determine whether cryptococcal meningitis is present.

8.4 Treatment of cryptococcal disease

Recommendations

- **We recommend that pulmonary cryptococcosis should be treated in the same way as CNS infection (Grade 1C), unless focal and not associated with hypoxia or a positive CSF examination.**
- **We suggest that pulmonary cryptococcosis, when focal and not associated with hypoxia or a positive CSF examination, may be treated initially with fluconazole 400 mg daily (Grade 2C).**

Treatment of pulmonary cryptococcosis is usually with a regimen recommended for cryptococcal meningitis that includes liposomal amphotericin B (see the CNS chapter of the BHIVA opportunistic infection guidelines [165]) [166]. Treatment with oral fluconazole (400–800 mg daily for the initial 10 weeks and 200 mg daily thereafter) is an alternative strategy if the cryptococcal antigen test is negative [166]. If the cryptococcal antigen test is positive but the CSF examination is negative and (i) there is no other evidence of dissemination, (ii) radiological infiltrates are focal and (iii) there is no evidence of hypoxia, some would consider fluconazole at 1200 mg daily as the induction dose when liposomal amphotericin B-based therapy is not used. However, all cases with moderate-to-high cryptococcal antigen levels (i.e. >1:160 by enzyme immunoassay) should be treated as per cryptococcal meningitis with liposomal amphotericin B-based regimens [173,174].

8.5 Prophylaxis for cryptococcal disease

Recommendation

- **We suggest that secondary prophylaxis can be discontinued after 1 year of cryptococcal therapy when the CD4 count is >100 cells/mm^3 and the individual has received ART with an undetectable HIV viral load for >3 months (Grade 2B).**

Primary prophylaxis with fluconazole is not recommended to prevent cryptococcal disease in people living with HIV with low CD4 counts in high-income countries. On the basis of data for cryptococcal meningitis, secondary prophylaxis can be discontinued when the CD4 count is >100 cells/mm^3 and the viral load has been undetectable for >3 months on ART and after the individual has received cryptococcal therapy for at least 1 year [175,176].

8.6 Impact of combination ART

The incidence of cryptococcal infection has declined dramatically with the widespread use of combination ART.

9 Aspergillosis

9.1 Background and epidemiology of aspergillosis

Aspergillus spp. colonise 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 people living with HIV [177]. IA is associated with severe immunocompromise. However, IA is rare in people living with HIV in the absence of other risk factors such as neutropenia, transplantation or glucocorticoid use. Chronic pulmonary aspergillosis is a chronic form of aspergillosis associated with chronic lung disease that may present as chronic cavitary pulmonary aspergillosis, chronic fibrosing pulmonary aspergillosis, aspergilloma (a fungal ball in a pre-existing cavity) or a pulmonary nodule [178]. An alternative presentation is subacute IA (formerly known as chronic necrotising aspergillosis, which shows a more rapid rate of evolution than other forms of chronic pulmonary aspergillosis and is associated with people who have mild degrees of immunocompromise, including people living with HIV) [178]. Chronic cavitary pulmonary aspergillosis was reported in approximately one-third of people living with HIV presenting with aspergillosis in a case series in the pre-ART era [179]. Aspergillosis may

also present in people living with HIV as tracheobronchial disease with obstructive features [180].

Risk factors for IA include neutropenia, resulting from medications, haematopoietic stem cell transplantation or malignancy, and corticosteroid use [180,181]. Chronic pulmonary aspergillosis is associated with COPD and other chronic lung diseases including cavitary disease due to TB [180]. Smoking marijuana and heavy alcohol consumption are also risk factors. Current understanding of IA in people living with HIV is based on evidence from a French national study of 242 cases of IA (74% with invasive pulmonary aspergillosis) in people living with HIV [182]. This study showed that, in the era of combination ART, approximately half of people with IA have traditional IA risk factors such as neutropenia while the remainder appear to have HIV-related risk factors. In addition, approximately half are receiving ART and, while a low CD4 count remains a risk factor, 18% have a CD4 count >200 cells/mm^3. A low CD4 count remains a significant risk factor for IA with the highest incidence in people living with HIV and a CD4 count <50 cells/mm^3 [183]. African origin has also been associated with an increased risk of aspergillosis in people living with HIV in the era of ART [184]. Cavitary TB is a risk factor for chronic pulmonary aspergillosis but as cavitary disease is less common in people living with HIV, the overall incidence of chronic pulmonary aspergillosis appears to be lower in people living with HIV than in individuals without HIV. In one study in Uganda involving 2 years of follow-up of people with TB, the prevalence of chronic pulmonary aspergillosis was 3.0% in people living with HIV compared to 6.7% in the control group without HIV [185].

9.2 Presentation of aspergillosis

Fever, cough and dyspnoea are common presenting features of IA and are often insidious in onset [186]. Pleuritic chest pain may occur. Haemoptysis is rare in people with IA. Cough and haemoptysis, observed in 42% of cases, are the typical presenting features of chronic pulmonary aspergillosis, while weight loss may also be observed [179]. A rare alternative syndrome described in people living with HIV is tracheobronchitis due to aspergillosis [187]. Individuals with tracheobronchitis have ulcerative or nodular lesions in the airway and usually have additional risk factors for aspergillosis such as neutropenia or glucocorticoid use. Clinical symptoms include fever, cough, dyspnoea, wheezing and stridor, and some cases may progress to IA.

9.3 Diagnosis of aspergillosis

Recommendations

- **We recommend that aspergillosis should be diagnosed by a combination of clinical, radiological and microbiological features. A histological sample can help exclude other conditions and increase the accuracy of diagnosis (Grade 1A).**
- **We recommend that special fungal staining such as KOH staining of sputum or BAL fluid and Grocott–Gomori methenamine silver or equivalent staining of biopsy specimens should be performed on all respiratory specimens from people living with HIV with pulmonary syndromes of undetermined aetiology (Grade 1C).**
- **We recommend that serum galactomannan can be used to aid the diagnosis of invasive pulmonary aspergillosis (Grade 1C).**
- **We suggest in cases being investigated for chronic pulmonary aspergillosis, BAL galactomannan or PCR can be combined with *Aspergillus*-specific IgG (Grade 2C).**
- **For subacute IA, we suggest that BAL galactomannan or PCR can supplement other tests (Grade 2C).**
- **We suggest that fungal culture should be requested on all samples as the definitive method of proving speciation (Grade 2B).**

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 [188]. Positron emission tomography with 18F-fluorodeoxyglucose is useful for diagnosis of invasive fungal infections, including invasive pulmonary aspergillosis, and increased uptake of 18F-fluorodeoxyglucose has been identified in lesions for up to 6 months after therapy has been initiated in immunocompromised patients without HIV [189].

Invasive pulmonary aspergillosis is identified when a compatible clinical syndrome is either associated with a biopsy specimen that demonstrates *Aspergillus* spp. by culture or histopathology or is associated with both a consistent clinical plus radiological appearance and with a positive microbiological sample from sputum or BAL fluid. Tracheobronchitis due to aspergillosis can be visualised by bronchoscopy.

The serum galactomannan test is an enzyme-linked immunosorbent assay that detects the presence of a cell wall constituent of *Aspergillus* spp. [190]. It is commonly used in people with haematological conditions, but few data are available in the setting of HIV.

False-positive results may occur in a variety of settings, including in individuals receiving piperacillin-tazobactam [191] and in people living with HIV with other invasive fungal infections such as histoplasmosis [192]. However there have been changes to the formulation of piperacillin-tazobactam in order to reduce the likelihood of false-positive results. Point-of-care galactomannan tests are being developed but often have moderate sensitivity and specificity [193].

Galactomannan [194] or PCR [195] may be used in BAL fluid but specific data for people living with HIV are limited. In cases being investigated for chronic pulmonary aspergillosis, BAL galactomannan or PCR can be combined with *Aspergillus*-specific IgG [196]. For subacute IA, BAL galactomannan or PCR can supplement other tests. Serum galactomannan has a low sensitivity in people without neutropenia explaining why these BAL tests have utility in these settings. Combinations of galactomannan and PCR in blood have also improved diagnosis in people at high risk of haematological conditions [197].

9.4 Treatment of aspergillosis

Recommendation

- **We recommend primary therapy with voriconazole for invasive or chronic pulmonary aspergillosis in people living with HIV (Grade 1B).**

On the basis of trials largely conducted in individuals without HIV, but including small numbers of people living with HIV, as well as a retrospective review of IA showing improved outcomes, voriconazole is the recommended agent to treat invasive/chronic pulmonary aspergillosis in people living with HIV [198]. Due to the declining incidence of IA, the newer antifungal agents such as voriconazole, isuvaconazole and caspofungin have not been directly compared or specifically studied in people living with HIV with aspergillosis. Voriconazole is administered at 6 mg/kg twice daily, as a loading dose for 24 hours, and then 4 mg/kg twice daily for at least 7 days, followed by 200 mg twice daily orally to complete 12 weeks' therapy. This regimen is superior to amphotericin B deoxycholate in the treatment of IA, as evidenced by improved response rates and decreased side effects [198], although this study did not compare voriconazole directly with liposomal amphotericin B and the primary statistical endpoint was evidence of non-inferiority. In the French national database of IA in people living with HIV, voriconazole use was associated with a significant reduction in mortality during the period 2002–2011 [182].

All azoles have significant drug–drug interactions in particular with ritonavir- and cobicistat-containing regimens and certain combinations need to be avoided [3,199]. Isavuconazole is a newer azole antifungal with activity against *Aspergillus* spp. In a large randomised controlled trial largely including people with haematological malignancy or who had undergone haematopoietic stem cell transplantation, non-inferiority was demonstrated versus voriconazole but isavuconazole was associated with fewer side effects [200]. In particular, isavuconazole was associated with a decrease in ocular, skin and hepatobiliary side effects which can be serious with voriconazole. At present there are no published data on the use of isavuconazole for IA/chronic pulmonary aspergillosis in people living with HIV and therefore recommendations cannot be made. Because isavuconazole is a cytochrome P450 (CYP)3A4 inhibitor, interactions will occur with protease inhibitors and other agents that are metabolised by this system [201]. It cannot be used with certain antiretroviral agents including tenofovir disoproxil fumarate/emtricitabine/elvitegravir/cobicistat, tenofovir alafenamide fumarate/emtricitabine/elvitegravir/cobicistat, darunavir/cobicistat or efavirenz. Treatment of chronic pulmonary aspergillosis must be individualised but prolonged courses of voriconazole are usually employed, sometimes combined with surgery on the basis of studies in individuals without HIV [178].

Liposomal amphotericin B 3 mg/kg once daily intravenously is currently the main alternative to voriconazole. Caspofungin, as a 70 mg loading dose and 50 mg once daily intravenously thereafter, is considered an option if neither voriconazole nor liposomal amphotericin B can be used and is the preferred agent if significant renal or hepatic disease is present [202]. When co-administered with efavirenz, the caspofungin dose needs to be increased to 70 mg [3]. Oral posaconazole solution 200 mg four times daily or 400 mg twice daily is another alternative to voriconazole or liposomal amphotericin B. In practice, individuals will usually receive treatment four times a day while in hospital, often with food supplements to enhance absorption. They can then switch to the twice-daily dosing when discharged home and are better able to tolerate a full meal, which is needed to optimise absorption with the twice-daily regimen. Therefore posaconazole oral solution is an alternative for individuals who are intolerant or resistant to standard therapy for IA [203]. Posaconazole tablets or solutions for intravenous administration are now alternative formulations dosed at 300 mg twice daily for 24 hours and 300 mg once a day thereafter.

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 twice daily or oral voriconazole 200 mg twice daily should be considered for chronic aspergillosis syndromes (conditions in which there is no evidence of parenchymal invasion) [204]. Azoles have multiple drug interactions therefore therapeutic drug monitoring should be performed to optimise dosing of voriconazole, posaconazole or itraconazole, with the timing guided by the formulation and drug [205]. Therapeutic drug monitoring may not be required for isavuconazole but more information is needed [206].

9.5 Prophylaxis for aspergillosis

Recommendation

- **We recommend that routine prophylaxis for pulmonary aspergillosis is not warranted (Grade 1C).**

9.6 Impact of ART

There is little information concerning trends in invasive pulmonary aspergillosis but the incidence appears to have declined in the post-ART era [207]. There have been case reports of individuals who have developed chronic necrotising pulmonary aspergillosis as IRIS following ART [208].

10 Cytomegalovirus (CMV)

10.1 Background and epidemiology of CMV

CMV is a double-stranded DNA virus and member of the human β-herpesviridae. CMV establishes latency and people living with HIV can develop disease due to reactivation. Occasionally disease is due to primary infection or superinfection and cases of primary infection presenting as CMV pneumonitis have been described in association with acute retroviral syndrome [209]. 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 fluid without evidence of end-organ involvement implies CMV infection but not disease. CMV isolation in BAL fluid (by culture or PCR) is common in people living with HIV with a low CD4 cell count [210,211]. The main risk factors for CMV pneumonitis are similar to those for other manifestations of

CMV end-organ disease. These include CD4 count <50 cells/mm^3, detectable HIV viral load, prior opportunistic infections and high CMV viral load in the blood [210]. CMV pneumonitis is often found in association with other CMV end-organ disease or other opportunistic infections [210,212]. The incidence of CMV end-organ disease has declined with ART although specific data for CMV pneumonitis are lacking [213].

10.2 Presentation of CMV

Typical symptoms of CMV pneumonitis are dry non-productive cough and exertional dyspnoea with fever; this presentation is similar to that of many other pulmonary conditions [210,214]. Hypoxaemia is often marked [210]. Chest radiographs and CT scans 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 be present [210,214,215]. There may be concomitant evidence of extra-pulmonary CMV [210] and a dilated eye examination should be performed to rule out CMV retinitis.

10.3 Diagnosis of CMV

Recommendation

- **We recommend that diagnosis of CMV pneumonitis requires a biopsy specimen to provide definitive evidence of pulmonary involvement in association with a compatible clinical syndrome (Grade 1C).**

The major diagnostic challenge is to differentiate CMV shedding in respiratory secretions from cases with CMV pneumonitis. Positive PCR for CMV from BAL fluid does not distinguish CMV shedding from pneumonitis, and hence must be interpreted with caution [216,217]. However, a negative culture result, with its high negative predictive value, does reasonably exclude CMV pneumonia [218]. Culture is now rarely performed in routine laboratory practice but diagnosis can be suggested by a compatible clinical and radiological pattern, absence of any other pathogen and supportive histopathological evidence such as multiple inclusion bodies or immunohistochemistry, where a biopsy is available [210]. High plasma CMV copy numbers detected by PCR increase the likelihood of CMV end-organ disease but lack sufficient sensitivity or specificity to establish the diagnosis without tissue samples [212].

10.4 Treatment of CMV

Recommendations

- **We recommend that the majority of individuals in whom microbiological tests on BAL fluid, or biopsy, demonstrate CMV should not receive treatment for CMV (Grade 1C).**
- **In cases with a compatible clinical syndrome and consistent microbiological or CMV PCR findings in the absence of any other pathogens, we recommend that anti-CMV treatment should be considered (Grade 1C).**
- **In individuals co-infected with other pathogens, it is reasonable to start by treating the co-pathogen first and to treat the CMV only if there is a failure of clinical response (Grade 1C).**
- **We recommend ganciclovir as standard therapy for CMV pneumonitis (Grade 1C).**

CMV replication in the respiratory tract is most frequently only a marker of immuno-suppression and CMV shedding, not of pneumonia.

These recommendations are supported by evidence that when treatment is withheld in individuals with evidence of CMV on BAL or biopsy, clinical outcome is not adversely altered [219,220]. However, for the select subset of individuals with evidence of a compatible clinical syndrome, positive microbiology and histology for CMV and no alternative diagnosis, the benefits of treatment have been suggested by retrospective case series that show improved clinical outcomes with treatment [211]. The management of individuals with positive histology for CMV but identification of a second pulmonary pathogen is also controversial.

Ganciclovir has been administered at 5 mg/kg twice daily intravenously for 21 days to treat CMV pneumonia [210]. However the optimal duration of treatment has not been established and some clinicians would treat for durations of 14–21 days depending on the response and severity. Foscarnet 90 mg/kg twice daily intravenously or cidofovir 5 mg/kg per week intravenously are alternatives for individuals who are not responsive or who are intolerant to ganciclovir therapy although data regarding CMV pneumonia in people living with HIV are limited. A small case series demonstrated good outcomes with foscarnet use, but was not able to provide microbiological evidence of CMV infection in all cases [221]. Oral valganciclovir 900 mg twice daily is a theoretical alternative for individuals able to tolerate oral therapy or for whom a switch from intravenous therapy is indicated but the evidence base for its use for treatment of CMV pneumonitis in people living with HIV is

currently limited.

Failure to respond to ganciclovir-based therapy can be related to immunosuppression, drug levels or development of resistance, or may suggest an alternative or concomitant diagnosis. The frequency of resistance has decreased in the era of combination ART as CMV resistance is associated with prolonged therapy. Reports of resistance to ganciclovir were primarily in the setting of CMV retinitis, and mutations in the *UL97* gene (phosphotransferase) were associated with low-level resistance while mutations in both *UL97* and *UL54* (DNA polymerase) genes were associated with high-level resistance [222]. *UL54* mutations can also lead to cidofovir and sometimes foscarnet cross-resistance. Several newer antivirals have been developed for the treatment of CMV but there are no specific data to guide their use in people living with HIV [223]. Maribavir inhibits UL97 and selects for a different pathway to resistance from ganciclovir so is predicted to have activity in the presence of resistance to other agents. Although maribavir has been studied primarily as pre-emptive therapy in transplant populations, it has demonstrated efficacy in a Phase 2 study of refractory or resistant CMV infections in a transplant setting and is associated with low rates of myelosuppression [224]. More recently maribavir has demonstrated superiority in the SOLSTICE Phase 3 trial versus investigator-assigned therapy (conventional therapy) in more than 350 haematopoietic or solid organ transplant recipients in terms of clearance of CMV in people with resistance or refractory disease to standard CMV therapy and was better tolerated than conventional therapy [225]. Brincidofovir is a DNA polymerase inhibitor related to cidofovir that was designed to be orally available and with less associated nephrotoxicity [223]. Although in theory brincidofovir has activity against *UL97*-resistant isolates, a clinical role in treatment is not yet established as initial trials in people post-transplant have focused on preventing rather than treating CMV. Similarly, letermovir is a CMV terminase inhibitor that has been licensed for prophylaxis of CMV in allogeneic haematopoietic stem cell transplant recipients [226] but its role in treatment of CMV infections is not yet established [223].

10.5 Prophylaxis for CMV

Recommendation

- **We recommend that valganciclovir may be considered as primary prophylaxis in selected people with persistent immunosuppression and detectable CMV DNA, or as secondary prophylaxis in those with relapse of CMV pneumonia after**

appropriate primary therapy (Grade 1C).

Although there is no clinical trial evidence to support the use of CMV prophylaxis, this may be considered in the exceptional person with a persistently low CD4 count, detectable CMV viraemia and no HIV treatment options. The vast majority of people with low CD4 cell counts will not require CMV prophylaxis. Valganciclovir prophylaxis (900 mg once or twice daily) can be considered in selected individuals when the CD4 count remains <50 cells/mm^3, there is persistent detection of CMV DNA or CMV viraemia, coupled with a low risk of prompt immune reconstitution by ART, and there is no evidence of CMV end-organ disease, because detection of CMV DNA is a risk factor for death in this setting over and above the risk of low CD4 cell count or HIV viraemia [227]. Maintenance therapy with valganciclovir is not initially required after treatment of CMV pneumonitis but may be added if CMV pneumonia relapses or if extra-pulmonary disease is present.

10.6 Impact of ART

ART has decreased the incidence of all forms of CMV end-organ disease [213] and CMV pneumonia is now rare. CMV IRIS occurs more commonly as an ocular complication, although there have been case reports of CMV IRIS in the lung [228].

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Appendix 1. Literature search strategies and PICO questions

Literature search strategies

Medline, Embase and the Cochrane Library were searched for English language publications between January 2010 and August 2020 using the following search terms:

PCP

(HIV OR AIDS OR immunocompromised) AND (Pneumocystis OR "P jiroveci" OR "P jirovecii" OR "P carini" OR "P carinii")

Bacterial pneumonia

(HIV OR AIDS) AND (((lower near/3 respiratory near/3 infection*) OR pneumonia OR (community near/3 pneumonia)) NOT ((Pneumocystis OR “P jiroveci” OR “P jirovecii” OR “P carini” OR “P carinii” OR tuberculo* OR “nontuberculous mycobacter*” OR “non-tuberculous mycobacter*” OR (mycobacter* near/3 infection*) OR “atypical mycobacter*” OR “avium complex” OR kansasi* OR cryptococc* OR “C. gattii” OR “C. neoformans” OR histoplasma* OR cytomegalo* OR (CMV near/3 infect*) OR (CMV near/3 virus) OR “human herpesvirus 5” OR “human herpes virus 5” OR HHV5 OR “HHV 5” OR ((influenza OR “influenza A virus” OR “influenza B virus” OR human near/3 influenza*) NOT (“H influenza*” OR “Haemophilus influenza*”)))

Influenza

(HIV OR AIDS) AND (influenza OR "influenza A virus" OR "influenza B virus" OR human near/3 influenza*)) AND (neuraminidase OR "neuraminidase inhibit[*3]" OR relenza OR zanamivir OR zanamavir OR tamiflu OR oseltamivir OR oseltamavir OR rapivab OR peramavir OR peramivir OR baloxavir))

(HIV OR AIDS) AND (influenza OR "influenza A virus" OR "influenza B virus" OR human near/3 influenza*)) AND (“antiretroviral therapy”) OR ("HAART" OR antiretroviral* OR (combin[*5] near/3 ART))

(HIV OR AIDS) AND (influenza OR "influenza A virus" OR "influenza B virus" OR human near/3 influenza*)) AND ("polymerase chain reaction" OR PCR OR “point of care” OR diagnos*)

Fungal pneumonias/CMV

(HIV OR AIDS) AND (cryptococc* OR "C. gattii" OR "C. neoformans")

(HIV OR AIDS) AND aspergill*

(HIV OR AIDS) AND (cytomegalo* OR (CMV near/3 infect*) OR (CMV near/3 virus) OR "human herpesvirus 5" OR "human herpes virus 5" OR HHV5 OR "HHV 5")

Abstracts from selected conferences (Conference on Retrovirus and Opportunistic Infections [CROI], International AIDS Society/International AIDS Conference, American Thoracic Society [ATS], European AIDS Conference [EACS], BHIVA, Infectious Disease Society of America [IDSA] and HIV Drug Therapy Glasgow) were also searched for the period 2017–2019.

PICO questions

PCP

What are the optimum treatment regimens for PCP in adults living with HIV?

What are the indications and the optimum prophylactic treatment of PCP in adults living with HIV?

When in relation to completing treatment for PCP in people living with HIV co-infection, should ART be started?

Are there any special considerations (e.g. pregnancy)?

Bacterial pneumonia

What is the aetiology of community-acquired pneumonia in people living with HIV?

How do people living with HIV present with community-acquired pneumonia?

Which empirical antimicrobial treatment strategy best reduces morbidity/mortality following diagnosis of community-acquired pneumonia in people living with HIV?

What is the utility of severity scoring systems in people living with HIV with community-acquired pneumonia?

What is the optimal vaccination strategy to prevent pneumococcal infection in people living with HIV?

Does the management of bacterial pneumonia in people living with HIV differ from those without HIV?

What is the role of vaccination against bacterial pneumonia in people living with HIV?

Influenza

What morbidity/mortality is associated with influenza A in people living with HIV on versus off ART?

Fungal pneumonias/CMV

What is the optimal diagnosis and management of suspected cryptococcal or *Aspergillus* spp. infection of the lung in people living with HIV?

What is the optimal diagnosis and management of suspected CMV pneumonia in people living with HIV?