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HIV GUIDELINES

# British HIV Association guidelines on the management of opportunistic infection in people living with HIV: The clinical management of non-tuberculous mycobacteria 2024

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## 1 | INTRODUCTION

A wide spectrum of non-tuberculous mycobacteria (NTM) has been reported as isolates from or causes of disease in people living with human immunodeficiency virus (HIV). This is typically in the context of very advanced immunosuppression (CD4 count <50 cells/mm$^3$) in the absence of virological suppression [1] and most individuals have presented with disseminated disease. Effective antiretroviral therapy (ART) has permitted control of viral replication, improvement in immune function and a significant decrease in the incidence of severe opportunistic infections [2–4], including disseminated *Mycobacterium avium* complex (DMAC) disease [3, 5, 6].

NTM are environmental organisms. Therefore it is important to determine, prior to treatment initiation, whether the organism is the cause of the disease process rather than a reflection of colonisation. With the exception of *M. avium* complex (MAC), there is limited evidence to guide the choice or duration of treatment and expert opinion should be sought from a clinician experienced in managing mycobacterial disease in the context of HIV or, if not available, in the context of immunosuppression or dissemination. Advice should also be sought from microbiologists (for drug susceptibility testing and interpretation), pharmacists or people with expertise and experience of managing mycobacterial disease in people without HIV. Also with the exception of MAC, most of the recommendations for the treatment of NTM have been extrapolated from trials of treatment for NTM pulmonary disease in individuals without HIV, although some evidence from early trials in populations with advanced HIV disease has added to this guidance.

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

A full review of these guidelines is due in 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 performed. 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.

## 3 | SUMMARY OF RECOMMENDATIONS

### From Section 5.4 Prophylaxis and impact of ART

- We suggest that primary prophylaxis against DMAC disease is not required for people with HIV and CD4 counts <50 cells/mm$^3$ if ART is initiated promptly (within 2 weeks from presentation) (Grade 2A).
- If MAC prophylaxis is used, we recommend stopping once ART is established and sustained virological suppression has been achieved (Grade 1A).
- We recommend prophylaxis against DMAC disease for individuals with CD4 counts <50 cells/mm$^3$ who are not taking ART, or for whom an effective antiretroviral regimen cannot be constructed (Grade 1A).
- For MAC prophylaxis, we recommend azithromycin 1250 mg once weekly or clarithromycin 500 mg twice daily (Grade 1A).

### From Section 5.5 Treatment of DMAC disease

- We suggest combination treatment including a macrolide and ethambutol, with rifabutin or rifampicin as first-line therapy for DMAC disease (Grade 2B).
- We recommend against macrolide monotherapy (Grade 1A).
- We suggest that either clarithromycin or azithromycin may be used as part of combination treatment, depending on tolerability and drug interactions (Grade 2D).
- We suggest that treatment for DMAC can be safely discontinued after at least 12 months, in those with clinical improvement, culture conversion and evidence of successful ART with undetectable viral load and CD4 count >100 cells/mm$^3$ for at least 6 months (Grade 2B).

### From Section 6.4 Diagnosis of *M. kansasii* disease

- We recommend that thorough investigation is undertaken if *M. kansasii* is isolated from a respiratory sample (Grade 1B).
- We recommend that at least three sputum samples should be collected (on different days or at least 12 hours apart) for the microbiological diagnosis of *M. kansasii* lung disease. If sputum samples cannot be obtained, one sample of induced sputum or bronchoalveolar lavage should be collected (Grade 1B).
- For all respiratory samples, we recommend that microscopy should be performed using auramine-phenol staining and samples should be cultured with liquid culture medium (Grade 1A).
- We recommend that molecular techniques should be used, rather than biochemical tests, for identification of *M. kansasii* culture isolates (Grade 1B).
- We recommend that interferon gamma release assays (IGRAs) should not be used for the diagnosis of *M. kansasii* disease (Grade 1B).
- We recommend routine baseline susceptibility testing of *M. kansasii* isolates for rifampicin only. In the case of rifampicin resistance, we recommend resistance testing of other agents for the treatment of *M. kansasii* (Grade 1B).

### From Section 6.5 Treatment of *M. kansasii* disease

- We recommend treating *M. kansasii* disease with a combination of rifampicin 600 mg/day, ethambutol 15 mg/kg/day and isoniazid 300 mg/day (plus pyridoxine) (Grade 1C).
- We recommend continuing treatment for *M. kansasii* pulmonary disease for at least 12 months after sputum culture conversion (Grade 1C).
- In the case of rifampicin resistance, we recommend that a regimen should be constructed on the basis of drug sensitivity testing results (Grade 1C).

## 4 | AUDITABLE OUTCOMES

- Proportion of people for whom MAC prophylaxis is only used when CD4 count is below 50 cells/mm$^3$ and this count is not expected to improve.
- Proportion of people with DMAC who are treated with at least two drugs from the outset including a macrolide unless contraindicated or the organism is resistant.
- Proportion of people for whom DMAC is confirmed by culture of blood or other fluid/tissue.

- Proportion of people with *M. kansasii* disease for whom resistance testing for rifampicin is performed.
- Proportion of people with *M. kansasii* disease who are treated with triple therapy as recommended unless contraindicated.

## 5 | MAC

### 5.1 | Background and epidemiology

MAC is the predominant NTM affecting people living with HIV, particularly those with advanced HIV disease and low CD4 counts. MAC organisms are present throughout the environment. Acquisition is via inhalation or ingestion of MAC bacilli through the respiratory or gastrointestinal tracts [7, 8]. No activity is known to predispose to infection, and person-to-person transmission is not believed to occur [9].

Prior to the use of effective ART with virological suppression, DMAC became clinically apparent in 20–40% of individuals with advanced HIV disease [1, 6], although a higher prevalence was detected at autopsy [10].

Since the widespread availability of modern ART, the incidence of DMAC has decreased [2, 5] and the prognosis has improved markedly [5]. In addition, the clinical presentation has changed to include immune reconstitution inflammatory syndrome (IRIS) [11].

### 5.2 | Clinical presentation of MAC infection (disseminated and localised)

DMAC typically occurs in those with advanced immunosuppression who have CD4 counts <50 cells/mm$^3$ without virological suppression. Symptoms are non-specific, and clinical signs and laboratory abnormalities may be similar to those of HIV progression or other HIV-related illnesses. Individuals with DMAC most commonly report fever, night sweats, diarrhoea, abdominal pain, fatigue and anorexia [12, 13]. Common signs include weight loss, hepatomegaly, splenomegaly and lymphadenopathy. Laboratory abnormalities include isolated anaemia or pancytopenia, which may be more severe than expected for the stage of HIV disease [8, 14], leukopenia, elevated alkaline phosphatase levels and hypoalbuminaemia [12, 13]. Radiological features commonly include hepatosplenomegaly and intra-abdominal lymphadenopathy, which were demonstrated in one case series using abdominal computed tomography in 14 of 17 individuals with DMAC [15]. Other focal physical findings or laboratory abnormalities may occur with localised disease, which can be the clinical presentation in individuals responding to ART. Focal manifestations described include palatal and gingival ulceration, septic arthritis, osteomyelitis, endophthalmitis, pericarditis and pulmonary and focal lymphadenitis [4, 16–24]. Localised syndromes, such as abscesses, new or worsening lymphadenitis, draining sinuses, intra-abdominal collections, skin disease or central nervous system (CNS) disease along with fever and systemic symptoms, may also be manifestations of IRIS [25].

### 5.3 | Diagnosis of DMAC disease

Diagnosis of DMAC requires culture from blood or a bone marrow aspirate or fluid from a normally sterile site or biopsy specimen, such as a lymph node. Mycobacterial blood cultures should be performed in any person living with HIV, not on ART, with a CD4 count <100 cells/mm$^3$ and fever or any other compatible symptom.

Culture of MAC from sputum or stool, in the absence of clinical or radiological features suggestive of disseminated infection, is insufficient to warrant antimycobacterial therapy. In some situations, given the time period required before cultures can be reliably deemed negative, empirical treatment may be considered pending these results. Experienced clinicians will ensure sufficient material has been received by the laboratory and is in culture before starting empirical treatment. Mycobacterial blood culture in liquid medium is usually only reported as definitively negative after 12 weeks' incubation, but very few cultures become positive after more than 6 weeks of incubation. Mean time to positive blood culture has been reported as 10–23 days (range 5–57 [26–29]) with only 2 of 47 cultures in one study becoming positive after 6 weeks' incubation [30]. The presence of NTM disease should be considered in people with long-term symptoms, anaemia, low CD4 counts, positive sputum culture results and when acid-fast bacilli (AFB) are seen on microscopy [31], although tuberculosis (TB) is an important differential diagnosis and must always be considered in designing an empirical treatment regimen or while awaiting organism identification from culture or direct molecular testing from primary samples. *M. tuberculosis* bacteraemia is associated with early mortality and must be treated promptly in unwell people [32].

Mycobacterial blood culture (standard and liquid) establishes the diagnosis of DMAC in 86–98% of

cases [33, 34]. Mycobacteraemia can be intermittent: one blood culture identifies 91% of people with MAC bacteraemia; a second blood culture increases the sensitivity to 98% [34]. Therefore, obtaining more than two sequential mycobacterial blood culture specimens to diagnose MAC bacteraemia is usually unnecessary [34].

The preferred culture method is lysis of peripheral blood leukocytes to release intracellular mycobacteria followed by inoculation onto solid medium (e.g. Lowenstein–Jensen or Middlebrook 7H11 agar) or into radiometric broth [31, 35]. Using the radiometric detection system, mycobacteraemia can be detected in 6–12 days, whereas a period of 15–40 days is required with solid medium. In addition, DNA probes can identify MAC species within 2 hours once sufficient mycobacterial growth has occurred [31, 36, 37]. Multiplex polymerase chain reaction (PCR) has also been shown to provide a low-cost alternative to DNA probe methods for rapid identification of MAC [38].

Biopsies from other, normally sterile, body sites may aid diagnosis. Stains of biopsy specimens from bone marrow, lymph node and liver may demonstrate acid-fast organisms or granulomas before positive blood culture results are obtained [39]. Although AFB staining of biopsy specimens is less sensitive than blood or bone marrow culture, it has been shown to be useful for the rapid diagnosis of DMAC infection permitting prompt initiation of antimycobacterial therapy [27]. DNA probes can also be applied directly to sputum, tissue or other body fluid specimens for rapid detection of MAC or *M. tuberculosis*, rather than waiting for sufficient bacterial growth in liquid medium [40].

In the absence of randomised clinical trials (and relevant also to people without HIV), the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines set useful criteria to distinguish between colonisation and disease for NTM pulmonary isolates [41] which have been adopted by the British Thoracic Society (BTS) [42] (see Table 1).

It is unknown whether NTM disease in people with HIV has the same predictors and risk factors as in those without HIV, and disease is often extrapulmonary. The ATS/IDSA [41] and BTS guidelines [42] do not specifically address NTM in people living with HIV, who are at higher risk of infection and for whom diagnostic criteria and clinical outcomes may have important consequences for differentiation between colonisation, subclinical disease and active disease.

In one observational study [23] in which NTM culture positivity in people living with HIV was categorised as infection versus colonisation, the authors concluded that NTM infection should be suspected in any individual with long-term symptoms, anaemia, low CD4 count and several positive sputum AFB cultures. The type of pathogen and the characteristics of the host may also be important factors in differentiating between colonisation and disease. When evaluating the possibility of disease, other important factors are the number of positive culture results and the number of bacteria (in colony-forming units [CFUs]) present in the sample [43].

**TABLE 1** Clinical and microbiological criteria for diagnosing NTM lung disease.

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|---|
| Clinical (both required): |
| 1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution CT scan that shows multifocal bronchiectasis with multiple small nodules. |
| 2. Appropriate exclusion of other diagnoses. |
| Microbiological (one of): |
| 1. Positive culture results from at least two separate expectorated sputum samples; if the results are non-diagnostic, consider repeat sputum AFB smears and cultures. |
| 2. Positive culture results from at least one bronchial wash or lavage. |
| 3. Transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathological features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM. |

Reproduced from *Thorax*, British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD), Haworth CS, Banks J, Capstick T et al., 72, ii1–ii64, 2017 with permission from BMJ Publishing Group Ltd.
Original source: Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; **175**: 367–416.
CT, computed tomography.

## 5.4 | Prophylaxis and impact of ART

Recommendations

- We suggest that primary prophylaxis against DMAC disease is not required for people with HIV and CD4 counts <50 cells/mm$^3$ if ART is initiated promptly (within 2 weeks from presentation) (Grade 2A).
- If MAC prophylaxis is used, we recommend stopping once ART is established and sustained virological suppression has been achieved (Grade 1A).
- We recommend prophylaxis against DMAC disease for individuals with CD4 counts <50 cells/mm$^3$ who are not taking ART, or for whom an effective antiretroviral regimen cannot be constructed (Grade 1A).

- For MAC prophylaxis, we recommend azithromycin 1250 mg once weekly or clarithromycin 500 mg twice daily (Grade 1A).

### 5.4.1 | Pre-ART studies

A series of randomised controlled trials and observational studies conducted in the pre-ART era demonstrated the value of MAC prophylaxis with rifabutin, clarithromycin or azithromycin in reducing the burden of disease in those with advanced HIV infection.

Two large randomised controlled trials [44] of daily rifabutin 300 mg versus placebo in individuals with advanced HIV disease and CD4 counts <200 cells/mm$^3$ showed rifabutin to be effective in reducing the incidence of MAC bacteraemia and of DMAC, but with little effect on overall survival [45]. Similarly, in a non-randomised clinical trial [46] including 536 participants with CD4 counts <100 cells/mm$^3$ (or CD4 counts <200 cells/mm$^3$ and an AIDS-defining condition), rifabutin was effective in the prevention or delay of MAC disease.

Clarithromycin and azithromycin were subsequently used in trials of similar designs for DMAC prevention. In the study by Benson et al. [47], 1178 participants with CD4 counts <100 cells/mm$^3$ were randomly assigned to clarithromycin or rifabutin alone or in combination. Clarithromycin was found to be more effective than rifabutin (risk ratio 0.56; 95% confidence interval [CI] 0.37–0.84 for clarithromycin *vs* rifabutin] and as effective as combination therapy, but associated with fewer adverse events.

Weekly azithromycin versus daily rifabutin, or a combination of these two agents, was compared in a randomised clinical trial in 693 participants with CD4 counts <100 cells/mm$^3$ [48]. Weekly azithromycin was more effective than rifabutin, with the incidence approximately halved in the azithromycin group (hazard ratio 0.53; 95% CI 0.34–0.85) compared with rifabutin. The combination of azithromycin and rifabutin was found to be more effective than azithromycin alone, but associated with an increase in adverse events and the potential for drug–drug interactions. Azithromycin-resistant isolates were detected infrequently (11%: 2 of 18 isolates) in those treated unsuccessfully with azithromycin, whereas resistant isolates were not detected in those receiving combination therapy where prophylaxis failed.

In the absence of a direct comparison, Chu et al. [49] made an indirect treatment assessment between these three drugs and found that the efficacy of rifabutin versus placebo ranged from 41% to 44%, while the efficacies of clarithromycin and azithromycin were estimated to be 73% and 72%, respectively. In a Cochrane review [50] of the efficacy of MAC prophylaxis, individuals treated with clarithromycin and azithromycin were 40% less likely to develop MAC disease than those treated with rifabutin. No statistically significant differences in survival were found between those receiving clarithromycin, azithromycin or rifabutin prophylaxis.

### 5.4.2 | Primary prophylaxis in the ART era

The availability of effective ART has radically reduced the risk of DMAC morbidity and mortality among people living with HIV [2–4]. One US-based study showed two cases of DMAC as a first opportunistic infection per 1000 person-years after 2010 [51].

This is mainly due to the rapid restoration of specific immune responses to MAC after initiation of effective ART, even in those with severe baseline immunodeficiency and only partial virological suppression [52].

Individuals with baseline CD4 counts <50 cells/mm$^3$ who are receiving ART but not MAC prophylaxis do not seem to be at increased risk of MAC disease, as reported in randomised clinical trials and in both prospective and retrospective observational studies [53–59]. In two large, randomised trials [53, 54] no significant differences in MAC incidence were found between participants taking azithromycin prophylaxis weekly compared with those taking placebo. All eligible participants had a previous CD4 count <50 cells/mm$^3$ and a sustained (>3 months) increase to >100 cells/mm$^3$ on ART. During the follow-up period (16 months) in the study by Currier et al. [53], there were two cases of MAC infection in the placebo group, compared with none in the azithromycin group, resulting in a treatment difference of 0.5 events per 100 person-years. In a trial by El Sadr et al. [54], in 153 participants with at least one CD4 count <50 cells/mm$^3$ who had commenced ART, the incidence of MAC disease was not statistically different between those receiving and those not receiving prophylaxis.

In a retrospective study [55] including 369 participants with CD4 counts <50 cells/mm$^3$ on ART, incidence rates of MAC infection (clinically or microbiologically diagnosed) were recorded over 6 months. At baseline, 65% of study participants had an HIV RNA viral load >10 000 copies/mL. The overall incidence of MAC infection while on ART was 0.6 per 100 person-months (7.2 per 100 person-years), with no significant differences between those receiving or not receiving prophylaxis. Eleven participants developed MAC infection during the 6-month period of observation, all with detectable HIV viral loads (>1000 copies/mL). No MAC infection occurred in those with an undetectable viral load at baseline.

In a large cohort study in the USA [56], risk of DMAC was investigated following the discontinuation of primary prophylaxis in individuals with CD4 counts maintained above 100 cells/mm$^3$. The proportion discontinuing prophylaxis increased from 16.7% in 1996 to 84.9% in 2002, with no increase in risk of blood culture-confirmed DMAC in those discontinuing prophylaxis after ART became generally available. Similarly, no case of DMAC was observed during a follow-up of 364 person-years in the Swiss HIV Cohort Study [57] among 253 individuals with nadir CD4 counts <50 cells/mm$^3$ who had been on ART for at least 3 months.

In a further US observational study by Dworkin et al. [58], the incidence of MAC was compared between those receiving ART but not MAC prophylaxis whose CD4 count had risen by at least 100 cells/mm$^3$ from baseline and those whose CD4 counts had not dropped below 50 cells/mm$^3$. The incidence of DMAC was low (one case per 100 person-years) among those whose CD4 counts had risen above the threshold of risk and not higher than in those whose CD4 counts had never decreased below this level.

These data highlight that primary MAC prophylaxis provides no additional benefit over ART for individuals with low nadir CD4 counts (<50 cells/mm$^3$) and is therefore not necessary provided that ART is started promptly (within 2 weeks of presentation) and where there is likely to be adequate immune reconstitution. However, primary prophylaxis against MAC should be considered in circumstances of very low CD4 counts and low likelihood of virological suppression, e.g. in individuals with a CD4 count <50 cells/mm$^3$, multidrug-resistant HIV and no ART option likely to lead to full virological suppression or ART adherence challenges. Primary MAC prophylaxis should also be considered in ART-naïve individuals with a CD4 count <50 cells/mm$^3$ where immune reconstitution is unlikely, or is likely to be delayed, due to comorbidities or concomitant immunosuppressive treatments, for example those with a new diagnosis of HIV and lymphoma who are starting chemotherapy.

When considering MAC prophylaxis, it is important to consider and to discuss with the person the risks and benefits of taking macrolides, the increase in pill burden and potential adverse effects of the drugs, the possibility of drug–drug interactions and the probable sequalae of acquired drug resistance due to inadvertent monotherapy in the case of active MAC disease or unmasking of MAC (IRIS). Where feasible, DMAC and other mycobacterial disease should be excluded prior to commencing prophylaxis, through clinical assessment and blood cultures, along with appropriate sampling of other sites if clinically indicated.

Of note, prophylaxis with clarithromycin or azithromycin has been associated with an increased incidence of macrolide-resistant bacterial colonisation of the respiratory tract [59]. Therefore people receiving prophylaxis presenting with lower respiratory tract infections should not be treated with macrolides.

For primary prophylaxis we recommend the use of one of the following agents:

- Azithromycin 1250 mg once weekly; or
- Clarithromycin 500 mg twice daily.

In the case of intolerance or allergy to macrolides, rifabutin 300 mg daily is an alternative option when prophylaxis is indicated. Dose adjustment may be necessary because of drug–drug interactions with ART.

We recommend stopping prophylaxis once sustained (>3 months) virological suppression has been demonstrated.

## 5.5 | Treatment of DMAC disease

- We suggest combination treatment including a macrolide and ethambutol, with rifabutin or rifampicin as first-line therapy for DMAC disease (Grade 2B).
- We recommend against macrolide monotherapy (Grade 1A).
- We suggest that either clarithromycin or azithromycin may be used as part of combination treatment, depending on tolerability and drug interactions (Grade 2D).
- We suggest that treatment for DMAC can be safely discontinued after at least 12 months, in those with clinical improvement, culture conversion and evidence of successful ART with undetectable viral load and CD4 count >100 cells/mm$^3$ for at least 6 months (Grade 2B).

### 5.5.1 | Introduction

In the pre-ART era, treatment of DMAC, initially with monotherapy [60] and then with combination therapy [61–63], was associated with short-term improvements in survival. Most of the literature on treatment is from the pre-ART or early ART eras and the benefits of modern, effective ART on longer-term survival are thus not shown in these studies.

Effective implementation of ART was strongly associated with prolonged survival after a diagnosis of MAC disease [64, 65] and it has been shown that treatment for DMAC could safely be discontinued once immune reconstitution has occurred [66]. Macrolide monotherapy [60, 67] and prolonged ineffective combination treatments without effective ART are associated with treatment-emergent macrolide resistance [68].

Frequent involvement of the gastrointestinal tract in DMAC leads to the potential for drug malabsorption. Drug–drug interactions between antimycobacterial and antiretroviral agents, as well as between these and other drugs, need to be considered when initiating and monitoring therapy.

### 5.5.2 | Combination treatment

In a randomised trial enrolling 160 individuals with DMAC [61], three treatment arms were evaluated: clarithromycin and ethambutol (CE); clarithromycin and rifabutin (CR); and clarithromycin with both ethambutol and rifabutin (CER). Although there were no statistically significant differences in the primary endpoint of microbiological response at week 12 (40%, 42% and 51% in the CE, CR and CER arms respectively), there were significant differences in survival and relapse in the triple-therapy CER arm compared with CR (relapse) and both dual-therapy arms (survival). A separate study evaluating the addition of rifabutin to clarithromycin and ethambutol [69] did not show improvement in response or survival, although there was a reduction in treatment-emergent macrolide resistance observed in the rifabutin group (2% *vs* 14% at 16 weeks of therapy). Addition of clofazimine to the combination of clarithromycin and ethambutol did not improve outcomes and was associated with higher mortality, with 61% versus 38% dying over 1 year of observation [62].

The combination of clarithromycin, ethambutol and rifabutin has been compared with rifampicin, ethambutol, clofazimine and ciprofloxacin, with the three-drug regimen associated with improved mycobacterial clearance from blood cultures (69% *vs* 29% over 16 weeks), reduced macrolide resistance and improved survival (median survival 8.6 *vs* 5.2 months) [70]. The combination of clarithromycin and clofazimine, compared with clarithromycin, rifabutin and ethambutol [68], showed the three-drug regimen to be associated with fewer clinical relapses and less emergent resistance. Clofazimine has also been studied in combination with clarithromycin, with or without ethambutol [71]. The three-drug regimen resulted in less resistance, reduced risk of relapse and longer time to relapse, although the study design did not permit differentiation between the effect of ethambutol in reducing resistance development as observed elsewhere and the effect of three-drug rather than two-drug therapy.

On the basis of evidence showing a reduction in the development of resistance and a possible survival benefit, we recommend three-drug therapy for most people for DMAC, which is still seen frequently in people with very low CD4 counts and without virological suppression. Three-drug therapy should include a macrolide, ethambutol and a rifamycin. The recommendation for three drugs would be particularly relevant in the presence of prolonged courses of treatment or in the absence of effective ART, to prevent resistance to macrolides.

Dosing is usually clarithromycin 500 mg twice daily or azithromycin 500 mg daily, with ethambutol 15 mg/kg and rifabutin 300 mg/day (adjusted for drug–drug interactions as necessary, using 150 mg daily) or rifampicin 10 mg/kg/day (see the University of Liverpool drug interactions tool: www.hiv-druginteractions.org). Two drugs, the macrolide and ethambutol, would be an alternative.

Macrolide susceptibility testing should be requested on the first positive culture isolate and, in case of macrolide resistance, we suggest seeking advice from experts in the treatment of MAC disease in the context of immunosuppression or dissemination. We also suggest liaising with mycobacterial reference laboratories with regard to identification and drug susceptibility testing.

Rifampicin, rather than rifabutin, has been used in MAC pulmonary disease and forms part of the recommendations of the BTS [42]; it has also been used in some smaller studies for HIV-associated DMAC [70, 72, 73]. However there has been no direct comparison with rifabutin to inform a recommendation within HIV infection. Extrapolating from data in people without HIV with pulmonary disease, we suggest that rifampicin may be used where rifabutin cannot be used. Indeed a recent meta-analysis showed that in comparison to rifabutin, rifampicin has at least similar treatment success rates in treating MAC [74].

### 5.5.3 | Which macrolide to use

Dunne et al. [75] compared azithromycin with clarithromycin for DMAC treatment, both in combination with ethambutol. Azithromycin was given at 250 or 600 mg once daily and clarithromycin at 500 mg twice daily. At 24 weeks, the rate of relapse was similar in the higher-dose azithromycin and the clarithromycin arms, but the lower-dose azithromycin arm was prematurely discontinued due to poorer performance in terms of mycobacterial blood culture conversion.

In a further study, participants were randomly assigned to azithromycin 600 mg or clarithromycin 1 g daily, both with ethambutol. Numbers of participants were low (37 in total), but mycobacterial cultures cleared in 86% of those taking clarithromycin, compared with 38% receiving azithromycin [76].

Azithromycin may have advantages over clarithromycin in terms of gastrointestinal tolerability and fewer drug–drug interactions. There is a bidirectional drug–drug

interaction between clarithromycin and rifabutin, with rifabutin exposure increased (potentially increasing the risk of uveitis) and clarithromycin exposure decreased (potentially decreasing efficacy). Anecdotally, and in the experience of the writing group, azithromycin is frequently used as the macrolide of choice in combination therapy with good efficacy.

### 5.5.4 | Dose of macrolide

In monotherapy and combination therapy studies, a range of doses of clarithromycin have been investigated. In monotherapy, a dose-ranging study of clarithromycin compared bacteriological clearance in terms of median CFUs per mL blood between doses of 500 mg, 1 g and 2 g, all given twice daily for 12 weeks to people with MAC bacteraemia [60]. The number of CFUs per mL decreased in all arms, but 11%, 33% and 29% of individuals were culture-negative in the 500 mg, 1 g and 2 g arms, respectively, at 2 weeks. Despite this, survival time was longest in the 500 mg arm. Clarithromycin resistance occurred in 46% of individuals who had positive cultures at 16 weeks, with no association between clarithromycin dose and risk of resistance.

In a study of clarithromycin with ethambutol, with either clofazimine or rifabutin by random allocation, clarithromycin was prescribed at 500 mg or 1 g twice daily. The higher dose of clarithromycin was discontinued due to a higher observed mortality (risk ratio 2.43; 95% CI 1.11–5.34) [77].

Clarithromycin at weight-based doses of 750 mg or 1 g, both given twice daily, showed similar efficacy but reduced tolerability in the higher-dose group [78].

The lower dose of 500 mg clarithromycin twice daily therefore appears to be as effective as higher doses and more tolerable. The dose of clarithromycin should therefore not exceed 500 mg twice daily, although care should be taken to still monitor for toxicity particularly QT interval prolongation.

Azithromycin has been used in fewer clinical trials; the 600 mg once daily dose has not shown evidence of excessive toxicity [75, 76]. A trial of azithromycin monotherapy, using 600 or 1200 mg once daily, reported fewer gastrointestinal adverse effects with 600 mg once daily and no increase in the number with sterilisation of blood cultures in the 1200 mg group compared with the 600 mg group [79]. Current tablet formulations mean that 500 mg is a more convenient dosing regimen.

### 5.5.5 | Other agents

Several other antimycobacterial agents have been studied in DMAC, although trials have been small and have seldom provided conclusive data about their possible role in treatment. Amikacin is sometimes used if there is treatment failure with oral therapy. Fluoroquinolones are the most frequently used alternative oral agents.

#### *5.5.5.1 | Amikacin*

Adding amikacin to a four-drug oral regimen of rifampicin, ciprofloxacin, clofazimine and ethambutol did not improve the response in terms of mycobacterial culture conversion [72]. As an intravenous induction therapy, amikacin with a macrolide, ethambutol and ciprofloxacin resulted in culture conversion in 13 of 15 participants, although the lack of a comparator arm and the small number of participants should be noted [80]. Evidence suggests an association between mitochondrial mutations (particularly the m.1555A>G mutation) and an increased risk of ototoxicity, although consideration of genetic testing should not delay the use of this drug if required. We suggest that amikacin should be reserved for situations in which oral therapy has been ineffective or is not feasible, for example in the intensive care unit.

#### *5.5.5.2 | Ciprofloxacin and newer fluoroquinolones*

A four-drug regimen containing rifampicin, ethambutol, clofazimine and ciprofloxacin did not shorten time to mycobacterial clearance compared with the three-drug regimen clarithromycin, ethambutol and rifabutin [70]. Ciprofloxacin has been used with ethambutol and amikacin, with high clearance rates in the first month of therapy [80]. In a non-randomised, observational study comparing outcomes in individuals receiving or not receiving ciprofloxacin as part of their MAC regimen, longer survival was observed among the former group [81]. In a further non-randomised study, ciprofloxacin with rifampicin, ethambutol and clofazimine showed a rapid reduction in CFUs, but there was no comparator arm [73]. Ciprofloxacin use as part of combination therapy has been described in several case series and reports [82, 83].

Newer fluoroquinolones such as moxifloxacin and levofloxacin are now recommended in guidelines for the treatment of drug-resistant TB and have been used, in particular, for refractory MAC pulmonary disease in people without HIV [42, 84].

There is *in vitro* evidence of susceptibility to moxifloxacin in MAC [85–87]. The use of moxifloxacin has been reported to have contributed to successful treatment in case reports of combination treatment for DMAC [11, 88], as has the use of levofloxacin [89–91].

In guidelines for the treatment of *M. tuberculosis*, levofloxacin is recommended in preference to

moxifloxacin because of reduced drug–drug interactions with rifampicin and a reduced risk of QT interval prolongation [92], although there is more experience in MAC pulmonary disease than in DMAC with levofloxacin.

#### 5.5.5.3 | *Linezolid*

There is little evidence for the use of linezolid for DMAC in people living with HIV and it is not licensed for this use. Although there is a degree of sensitivity demonstrated *in vitro* [87], published clinical experience is limited to case reports of MAC pulmonary and extrapulmonary disease in people without HIV [93, 94]. We suggest that linezolid may be considered as part of combination therapy where first-line therapy has failed or is contraindicated, with close monitoring due to related toxicity.

#### 5.5.5.4 | *Bedaquiline*

There is *in vitro* evidence of bedaquiline efficacy against NTM (including *M. avium*) [95, 96]. Like linezolid, it has been used in MAC pulmonary disease in individuals without HIV and is given as an option in this setting in the BTS guidelines [42].

However, there is only limited experience in the treatment of MAC disease and in particular in the setting of disseminated infection in HIV. Literature searches identified only case reports in which bedaquiline use, in combination with other agents, was successful in treating MAC disease [97].

Of note, bedaquiline concentrations are reduced when given in combination with rifamycins (in particular rifampicin and rifapentine) [98, 99], and usually co-administration is not recommended. However in a pharmacokinetic study in healthy volunteers, steady-state rifabutin resulted in little quantitative impact on bedaquiline exposure, but was associated with more adverse events [100].

We suggest that bedaquiline may be considered as part of combination therapy where first-line therapy has failed or is contraindicated, with close monitoring due to potential increased toxicity.

#### 5.5.5.5 | *Clofazimine*

Clofazimine has not historically been recommended in first-line regimens for HIV-associated DMAC because of the observed higher mortality in the study by Chaisson et al., published in 1997 [62]. In that study, clofazimine, added to the dual regimen of clarithromycin and ethambutol, was associated with 61% versus 38% mortality among the 106 participants, despite higher baseline colony counts in the three-drug arm and better culture conversion. Monitoring of QT interval (using clarithromycin and clofazimine together) was not reported. Comparing with other pre-ART-era DMAC studies described earlier, there was no excess mortality with clofazimine in the study by May et al. [68], although the clofazimine-containing dual therapy was not as effective as the current standard clarithromycin, rifabutin and ethambutol triple therapy. In the study by Shafran et al. [70], clofazimine formed part of a three-drug regimen with no macrolide, compared with a four-drug regimen with a macrolide, and there were more relapses and reduced duration of survival in the three-drug, macrolide-free regimen.

Since then, clofazimine has been used in the treatment of drug-resistant TB, for people with and without HIV, and there has been no published mortality excess, although there has not been a clear randomised comparison of clofazimine versus a clofazimine-free regimen [92, 101–104].

In summary, the decreased survival associated with a clofazimine-containing regimen in the 1997 trial has not been clearly replicated elsewhere and clofazimine is a standard part of recommended regimens for drug-resistant TB for people with and without HIV [92]. The writing group considered it reasonable to include clofazimine, with appropriate monitoring including that of QT interval, in regimens for macrolide-resistant DMAC or in other situations in which it is needed to construct an effective regimen.

### 5.5.6 | Duration of treatment and secondary prophylaxis

Until the advent of effective ART, lifelong continuation of combination therapy for MAC was recommended, although life expectancy was short with a median survival of less than 1 year [105].

Small, observational studies showed prolonged relapse-free survival among those receiving ART with CD4 counts rising to above 100 cells/mm$^3$, clinical improvement in MAC disease and no evidence of relapse [106–108]. A non-randomised, interventional study included 48 individuals with DMAC who stopped treatment after a median of 31 months using criteria of at least 12 months of treatment, sterile mycobacterial cultures, at least 16 weeks of ART and two consecutive CD4 counts >100 cells/mm$^3$. Over a median follow-up of 77 weeks, there was a low incidence (1.44 per 100 person-years) of relapse [66].

In a study in Taiwan, fewer people stopped treatment when CD4 count was >100 cells/mm$^3$ with the majority having an undetectable HIV RNA level and experiencing no relapses over the following 12 months [109]. Retrospective studies from Canada [110] and France [111] supported the finding of a very low risk of relapse when therapy for DMAC was stopped after 12 months in those with improvements in CD4 counts while receiving ART.

An analysis of European cohort studies evaluating interruption of secondary prophylaxis for a range of opportunistic infections [112] included 379 interruptions of treatment, of which 103 were for MAC, with a median CD4 count (at interruption) of 190 cells/mm$^3$ (interquartile range [IQR] 129–290), with 86% of individuals interrupting with CD4 counts >100 cells/mm$^3$. Not all (80%) participants had an undetectable HIV RNA level, but the median duration of therapy before interruption was 23 months (IQR 12–31 months). There were two relapses during follow-up, one in an individual whose prophylaxis was stopped with a CD4 count <100 cells/mm$^3$ and one in an individual whose secondary prophylaxis was stopped with a CD4 count >100 cells/mm$^3$ for only 8 months, with an overall incidence of MAC relapse of 0.9 per 100 person-years (95% CI 0.11–3.25).

The Swiss HIV Cohort Study reported a retrospective review of 24 individuals discontinuing MAC treatment, with no recurrence over 29 months of follow-up (upper limit of 95% CI 5.3 per 100 person-years), although there were two deaths from other causes [65]. A UK-based study of 15 participants with DMAC revealed no relapses on cessation of MAC treatment once CD4 counts were >100 cells/mm$^3$, after a median treatment duration of 29 months [113].

These small studies are consistent in their findings and we therefore recommend that treatment for DMAC can be discontinued with very low risk of relapse after at least 12 months of treatment, culture conversion, evidence of effective and ongoing ART for 6 months and CD4 counts of at least 100 cells/mm$^3$.

With more recent effective ART, the view of the writing group, in the absence of published studies, is that with clinical improvement, good immune reconstitution (confirmed CD4 count >100 cells/mm$^3$), culture conversion and undetectable HIV viral load, individuals should be able to safely discontinue MAC treatment after 6 months. If the CD4 count falls to <50 cells/mm$^3$, MAC prophylaxis should be recommenced.

### 5.5.7 | Starting ART

There have been no trials comparing ART regimens in DMAC. In terms of when to start ART, we suggest referring to the BHIVA antiretroviral treatment guidelines, which recommend, based on the ACTG 5164 study [114] (which notably only included 10 participants with mycobacterial infections), that ART is commenced within 2 weeks of specific antimicrobial chemotherapy in ART-naïve individuals with major opportunistic infections [115]. We also recommend referring to the BHIVA TB guidelines [116] for studies of the timing of ART in TB in people who are ART naïve. Several high-quality studies have demonstrated mortality benefit from starting ART within 2 weeks of antimycobacterial therapy in those with CD4 counts <50 cells/mm$^3$ [117–119]. Although IRIS occurred, it was manageable and not associated with excess mortality. Drug interactions were manageable.

For those already receiving ART, this should be continued if effective, changed based on resistance tests if there is evidence of virological failure or adjusted to manage drug–drug interactions.

Drug–drug interactions and tolerability, as well as tablet burden, will be the key concerns in choosing ART for those receiving concurrent treatment for DMAC. We recommend using the University of Liverpool drug interactions tool (www.hiv-druginteractions.org) and suggest that integrase inhibitors may be preferred third agents. If protease inhibitors are needed, rifabutin dose should be reduced accordingly. If non-nucleoside reverse transcriptase inhibitors (NNRTIs) are used, dose adjustment of both rifabutin and the NNRTI might be needed (e.g. double dosing of doravirine in combination with rifabutin, or increased dose of rifabutin in combination with efavirenz).

## 6 | *M. KANSASII*

### 6.1 | Epidemiology

*M. kansasii* is a slow-growing NTM, widely distributed in the environment [41]. Infections caused by *M. kansasii* have been associated with exposure to contaminated municipal water systems, as this organism thrives in human-engineered environments, with the major reservoir being tap water. Infection is mostly acquired through the aerosol route and may cause disease in both immunocompetent and immunosuppressed individuals [120]. Human-to-human transmission is not thought to occur [121].

*M. kansasii* is the second most common cause of NTM disease in European countries (including the UK), the USA, South America and China [122], often occurring in geographic clusters. In Europe, Poland has the highest *M. kansasii* isolation rate (35% of all NTM in Poland *vs* 5% in Europe overall) [122]. In a retrospective study conducted in California during the pre-ART period (1992–1996), the incidence of *M. kansasii*-positive respiratory isolates was found to be 647 per 100 000 in persons with AIDS versus 115 per 100 000 in people living with HIV (but without AIDS) and 0.7 per 100 000 in the general population [123].

Up-to-date data on the incidence of *M. kansasii* infection in people living with HIV in the current ART era are lacking. It is thought to remain the second most common

species of NTM to cause disease in people living with HIV, after MAC [124–126].

## 6.2 | Risk factors and mortality

Immunosuppression associated with HIV is one of the most important risk factors for *M. kansasii* infection. Other well-recognised risk factors are the presence of lung disease [127] (in particular chronic obstructive pulmonary disease, previous pulmonary TB and pneumoconiosis), chronic liver disease, excessive alcohol consumption, haematological disease, malignancy and other forms of immunosuppression (e.g. prolonged steroid treatment and organ transplantation) [128].

Of interest, a study in miners, who have additional NTM risk factors, demonstrated that *M. kansasii* pulmonary disease occurred at an earlier stage of HIV infection and more closely resembled disease in people without HIV than in other settings [129]. In a more recent study conducted in Korea, working in heavy industry and presence of a low body mass index were also found to be independent risk factors for the development of *M. kansasii* lung disease [130].

*M. kansasii* is associated with a higher mortality than other types of NTM [131], including in people living with HIV [132]. In a retrospective study of South African gold miners [129] treated for *M. kansasii* infection, mortality rates of 2% were found in individuals without HIV versus 9% in those with HIV. Both ART and therapies for *M. kansasii* have been shown to be associated with increased survival [132]; factors that predicted mortality in people living with HIV with *M. kansasii* pulmonary disease were presence of a lower CD4 cell count, lack of ART, positive sputum smear microscopy and a lack of adequate mycobacterial treatment.

## 6.3 | Presentation of *M. kansasii* disease

### 6.3.1 | Clinical manifestation of pulmonary disease

Unlike MAC disease, *M. kansasii* in people living with HIV more commonly presents with localised pulmonary disease than with disseminated features [133–135]. Isolated bacteraemia is present in only a small proportion of people with HIV affected by *M. kansasii* (approximately 10%), and disseminated disease is seen generally in those with advanced HIV infection [41].

*M. kansasii* pulmonary disease mimics the course of TB; the most typical presenting symptoms are fever, cough, sputum production, weight loss and breathlessness. Other presentations include chest pain, haemoptysis and increased sweating [121].

People with HIV and *M. kansasii* lung disease present with diverse radiographic patterns, most commonly consolidation and nodules, predominantly located in the middle and lower lung zones. This finding is in contrast to the upper lobe cavitary presentation described in those without HIV infection. Interstitial infiltrates and hilar lymphadenopathy are common, and with higher CD4 counts there is an increased risk of cavitary disease. Rarely, pulmonary disease can manifest with endobronchial lesions [136, 137]. In a study of HIV-associated *M. kansasii* lung disease [138], abnormal chest radiographic results were found in 90% of people (75/83). Consolidation (66%) and nodules (42%) were the most frequent findings, with middle or lower lung zones involved in 89% of individuals. The pattern of radiographic abnormalities did not differ based on AFB smear status, the presence or absence of coexisting pulmonary infections or CD4 count. Cavitation was the only radiographic abnormality independently associated with mortality (hazard ratio 4.8).

### 6.3.2 | Clinical manifestations of extrapulmonary disease

Common sites of extrapulmonary disease include lymph nodes, skin and the musculoskeletal and genitourinary systems. Pericarditis with cardiac tamponade, oral ulcers and chronic sinusitis have also been reported in people with AIDS. CNS disease can occur and most commonly manifests as meningitis. People with CNS infection have high rates of morbidity and mortality despite appropriate treatment. Infection of the spine is exceedingly rare, with few reported cases [139].

Isolated musculoskeletal disease is rare, with monoarticular synovitis and osteomyelitis reported following trauma to the involved joint, or bones and joints being sites of infection with disseminated disease [140]. Cutaneous lesions caused by *M. kansasii* have been described and most commonly manifest in the setting of concomitant pulmonary disease or disseminated infection [141]. The lesions are generally subacute or chronic in nature and require skin biopsy for histopathological and microbiological assessment.

## 6.4 | Diagnosis of *M. kansasii* disease

- We recommend that thorough investigation is undertaken if *M. kansasii* is isolated from a respiratory sample (Grade 1B).
- We recommend that at least three sputum samples should be collected (on different days or at least

12 hours apart) for the microbiological diagnosis of *M. kansasii* lung disease. If sputum samples cannot be obtained, one sample of induced sputum or bronchoalveolar lavage should be collected (Grade 1B).
- For all respiratory samples, we recommend that microscopy should be performed using auramine-phenol staining and samples should be cultured with liquid culture medium (Grade 1A).
- We recommend that molecular techniques should be used, rather than biochemical tests, for identification of *M. kansasii* culture isolates (Grade 1B).
- We recommend that interferon gamma release assays (IGRAs) should not be used for the diagnosis of *M. kansasii* disease (Grade 1B).
- We recommend routine baseline susceptibility testing of *M. kansasii* isolates for rifampicin only. In the case of rifampicin resistance, we recommend resistance testing of other agents for the treatment of *M. kansasii* (Grade 1B).

Diagnosis of *M. kansasii* pulmonary disease can be made using sputum samples, induced sputum, bronchoalveolar lavage and bronchial washings [42]. More invasive techniques, such as the use of transbronchial biopsies, may be helpful but are associated with increased procedural risks.

The process of investigating for *M. kansasii* pulmonary disease is the same as for *M. tuberculosis* and we recommend collecting at least three sputum samples (on different days or at least 12 hours apart). If sputum samples cannot be obtained, one sample of induced sputum or bronchoalveolar lavage should be collected.

*M. kansasii* is a virulent species, and isolates in cultures of respiratory samples from individuals without HIV have been found to be clinically relevant in more than half of cases [142–145].

There is uncertainty whether a single positive respiratory culture for *M. kansasii* in the context of HIV should be considered clinically relevant; some authors interpret a single positive *M. kansasii* respiratory isolate as an indicator of disease [133, 146–148] as *M. kansasii* is among the most pathogenic of NTM species. Repeated positive isolates may signify active disease even in the absence of new symptoms.

Given the high pathogenicity of this species, we recommend full investigation of people even with a single positive *M. kansasii* isolate from a respiratory sample, with a decision on whether to initiate therapy made on the basis of the clinical presentation. For instance, in people in whom *M. kansasii* is isolated from non-sterile sites, in the absence of clinical and/or radiological disease, specific therapy should be withheld. In the case of repeated positive cultures with negative smear microscopy in those who are asymptomatic, a watchful approach is recommended, especially in the presence of virological control and a high CD4 count [132]. Conversely, the finding of *M. kansasii* in sterile body locations, such as blood, tissue, cerebrospinal fluid, pleural fluid and brain, should be considered clinically significant.

Microbiological detection methods have a relatively high sensitivity and specificity for the detection of localised NTM infections in people with HIV. In a population-based study, 41% of individuals affected by *M. kansasii* were sputum smear-positive. Cultural pathogen detection had a high positive predictive value for clinically relevant infection: 85.7% and 71.4% in individuals with and without HIV respectively [123].

For all respiratory samples, microscopy and culture should be performed, as this remains the most sensitive way to detect NTM. Microscopy should be performed using auramine-phenol staining, which allows for enhanced sensitivity compared with the Ziehl–Neelsen method. Samples should be processed as soon as possible and within 24 hours to avoid bacterial overgrowth; the sputum samples should be refrigerated if delays longer than 24 hours are anticipated [42].

We recommend the use of liquid culture medium for isolation of *M. kansasii*; liquid culture is increasingly being used globally as the reference standard, including in settings with high HIV prevalence [149].

The use of molecular techniques can aid in the early detection of NTM versus *M. tuberculosis* [150], and should always be used as an adjunct to cultures. Of the molecular techniques available, line probe assays are commonly used in the UK and are useful for the rapid identification of the most common types of NTM. Although specific PCR tests are available for *M. kansasii* [151], there is a lack of validation in people living with HIV and they are less sensitive than conventional AFB culture. Moreover, false-positive PCR results [152] for *M. avium* and *M. kansasii* have been reported in the presence of other species of NTM (*M. scrofulaceum* and *M. flavescens* respectively) due to the similarity in the hypervariable region A of 16S RNA.

IGRAs have been found to be positive, although at a low rate, in those with *M. kansasii* infection, which carries some of the *M. tuberculosis*-specific antigens adopted for IGRAs [153]. IGRAs should not be used for diagnosing active *M. kansasii* infection, as this method does not distinguish between active disease and latent infection.

Routine susceptibility testing of *M. kansasii* isolates should be performed for rifampicin only [154]. Resistance to rifampicin correlates well with treatment failure for *M. kansasii* [155]; moreover, when there is resistance to isoniazid and ethambutol, it is generally in the presence of rifampicin resistance [156].

In the case of rifampicin resistance, we recommend testing potential secondary agents, which include amikacin, ciprofloxacin, clarithromycin, ethambutol, rifabutin, streptomycin, sulphonamides and isoniazid, for the treatment of *M. kansasii*. *In vitro* minimum inhibitory concentrations of agents against *M. kansasii* are near the peak achievable serum levels and more than 100-fold greater than the values for *M. tuberculosis*. As the concentrations of anti-tuberculous drugs used in susceptibility testing are based on *M. tuberculosis* tests, some isolates of *M. kansasii* may be reported as resistant to isoniazid at 0.2 g/mL, while the 1 g/mL standard concentration may yield variable results [157]. These isolates are in fact susceptible to slightly higher drug concentrations, and reports of resistance to the low concentrations of isoniazid have no clinical or therapeutic significance as long as a regimen containing rifampicin is used [41].

## 6.5 | Treatment of *M. kansasii* disease

- We recommend treating *M. kansasii* disease with a combination of rifampicin 600 mg/day, ethambutol 15 mg/kg/day and isoniazid 300 mg/day (plus pyridoxine) (Grade 1C).
- We recommend continuing treatment for *M. kansasii* pulmonary disease for at least 12 months after sputum culture conversion (Grade 1C).
- In the case of rifampicin resistance, we recommend that a regimen should be constructed on the basis of drug sensitivity testing results (Grade 1C).

There have been no randomised clinical trials to demonstrate the optimal treatment for *M. kansasii* disease [133] and the available studies offer limited data in people living with HIV.

It has been shown that inclusion of rifampicin in the regimen permits faster culture conversion with a lower risk of relapse in those with *M. kansasii* pulmonary disease [133]. Before the advent of rifampicin, only 52–80% of people achieved sputum conversion at 6 months, with relapses in ~10% and a frequent need for surgical resection [158]. With rifampicin-containing regimens, culture conversion generally occurs within the first 4 months of treatment [158–160], with treatment failure and long-term relapse in ~1% of cases if treatment is maintained for at least 12 months [161].

We recommend, in line with the ATS/IDSA [41] and BTS guidelines [42], treating *M. kansasii* infection with a combination of three antimycobacterial drugs, including rifampicin 600 mg/day, ethambutol 15 mg/kg/day and isoniazid 300 mg/day plus pyridoxine.

In two retrospective cohort studies with small numbers of participants [162, 163], similar cure rates (80–100%) were achieved with clarithromycin instead of isoniazid.

A macrolide (such as azithromycin 500 mg daily or clarithromycin 500 mg twice daily) can be used as an alternative to isoniazid. Azithromycin is preferred to clarithromycin due to the lower incidence of drug–drug interactions with antiretroviral agents, although clinical data on its efficacy are limited.

Rifabutin may be used as an alternative to rifampicin to reduce the impact of drug–drug interactions, particularly in the case of ART including a boosted protease inhibitor. In the case of resistance or intolerance, rifamycins can be replaced by moxifloxacin [41].

No randomised clinical trials have evaluated the optimal duration of treatment for *M. kansasii* pulmonary disease or disseminated disease in people living with HIV. The duration of treatment should be at least 12 months following sputum culture conversion. In the event that people are not able to produce subsequent sputum samples while on treatment, the total duration of treatment can be 12 months, as long as there has been clinical improvement. In pulmonary infections with initially positive sputum isolates, samples should be re-checked routinely (mycobacterial culture) after starting treatment, every 4–12 weeks during treatment, and for 12 months after completing treatment to assess the microbiological response [42]. Treatment failure should be considered in the case of culture conversion failure within 4 months and/or a lack of clinical and radiographic improvement.

*M. kansasii* infection can be challenging to treat given the need for multiple drugs and long treatment periods giving rise to additional complications, including pill burden, adherence difficulties, potential drug interactions and adverse events [164]. Regular assessment of adherence, addressing barriers such as side effects and provision of ongoing support to maintain adherence are needed. In the case of therapeutic failure, isolates should be tested against a wide panel of antibiotics to guide new treatment regimens.

Although treatment for 12 months with at least three drugs is effective for the majority of cases of *M. kansasii* lung disease, it has been shown to be insufficient for some. Treatment for 18 months has been associated with lower relapse rates compared with shorter treatment periods (9 or 12 months) [161].

*M. kansasii* isolates that have become resistant to rifampicin as a result of previous therapy have been treated successfully with a regimen that consists of high-dose daily isoniazid (900 mg) with pyridoxine (50 mg/day), high-dose ethambutol (25 mg/kg/day), and sulfamethoxazole (1.0 g three times daily) combined with daily or

five times per week streptomycin or amikacin for the initial 2–3 months, followed by intermittent (twice weekly) streptomycin or amikacin for a total of 6 months [156].

There is no recommended prophylaxis or suppressive regimen for disseminated *M. kansasii* disease.

## 7 | NTM MINOR SPECIES

### 7.1 | Epidemiology

More than 170 species of NTM that cause human disease have been described, the most important of which are MAC and *M. kansasii*. Among the remaining minor species, the most frequently described infections in people living with HIV include *M. chelonae/abscessus*, *M. fortuitum*, *M. gordonae*, *M. simiae* and *M. genavense* [165].

### 7.2 | Risk factors and mortality

As with MAC and *M. kansasii*, immunosuppression due to HIV remains one of the most important risk factors for infection with minor species of NTM. In a retrospective series of 297 NTM infections in Germany, 87 (29.3%) were observed in people living with HIV, 56 (64.4%) of whom had CD4 counts <50 cells/mm$^3$ [166]. In a similar series from Portugal, 66.2% of 74 NTM infections were seen in people living with HIV [167]. In Southeast Asian countries, the prevalence of NTM infection among 1060 people living with HIV was estimated at 2%, with current ART conferring lower odds of NTM infection [168]. In China the prevalence of NTM infection in people living with HIV with positive mycobacterial cultures was 47%, with a diagnosis of NTM versus TB being significantly associated with lower median CD4 counts [169]. In a case-finding study from Ghana, 8% of 473 positive mycobacterial cultures isolated from people living with HIV were sequenced as NTM, with NTM infection versus TB being associated with CD4 counts <100 cells/mm$^3$ [170]. In the USA, the median annual incidence of NTM infection in people living with HIV derived from laboratory records was estimated at 110 per 100 000 persons, rising to 5300 per 100 000 in people with a CD4 count <50 cells/mm$^3$ [171]. Among 36 case reports of NTM infection among people living with HIV, only five were from people with CD4 counts >100 cells/mm$^3$ [172–176].

Due to the spectrum of infecting species and clinical syndromes, it is difficult to generalise about the outcomes and mortality associated with NTM infection. It is clear, however, that survival of people living with HIV who have NTM infection has increased markedly with the advent of ART. For example, in an international case series reported in 1995, in the pre-ART era, 76% of 54 people with *M. genavense* infections who were living with HIV had died by 1 year, with none surviving beyond 21 months [177]. By contrast, a retrospective case series of 25 *M. genavense* infections diagnosed in individuals who were living with HIV, from 19 centres in France and following the introduction of ART, reported markedly reduced mortality rates of 26% at 1 year and 50% at 5 years [178].

Respiratory infections account for up to 90% of all NTM isolates implicated in clinical disease, although there is often uncertainty as to whether the presence of NTM in respiratory samples represents colonisation or infection [169, 179]. For example, in a series of 291 NTM isolates recovered from 202 people between 2001 and 2010, less than half (46%) of 24 different NTM species were associated with human disease, and only a minority with pulmonary isolates met ATS diagnostic criteria for NTM disease [180]. In the USA, only 39% of people with pathogenic NTM isolated from bronchoscopic sampling after admission to hospital with pneumonia met ATS diagnostic criteria for NTM pulmonary disease [181].

Disseminated infections with NTM species isolated from blood cultures have also been reported; isolation of NTM species from blood culture was described in nearly two-thirds (62.5%) of individuals included in a case series [182]. A wide range of other extrapulmonary presentations are also recorded in case series and case reports, including vertebral osteomyelitis [183–185], cutaneous infection [186–189] and CNS infection [190–193]. Of note, *M. genavense* is particularly associated with complex gastrointestinal syndromes, including retractile mesenteritis [194–197]. Finally, it is important to be aware that NTM infection is also frequently implicated in the presentation of IRIS in people who are living with HIV [198–201].

### 7.3 | Diagnosis and treatment of NTM minor species

Despite their ubiquity, there is currently no high-quality evidence on which to base guidance on the diagnosis and treatment of infection with minor species of NTM. The literature review conducted for these guidelines yielded 115 citations that addressed NTM disease. These included 37 case reports, 46 case series, 10 reports described as cross-sectional, prevalence or incidence studies and 11 studies with various other epidemiological designs. The remainder consisted of narrative reviews, personal opinion or other articles that did not present either primary data or secondary data analyses. Fewer than half of

identified citations (53; 46.1%) were concerned specifically with NTM infection in people living with HIV; the majority of these were case reports (36; 67.9%). There were no randomised or otherwise controlled studies comparing outcomes from different treatments.

### 7.3.1 | Diagnosis

When making a diagnosis of infection with NTM minor species, it is important to be aware that speciation does not allow for assumptions of susceptibility to antimycobacterial treatment. Where there is a clinical suspicion of disease, phenotypic drug sensitivity testing should be performed on all isolates, where possible. When susceptibility testing is performed, this should include, at a minimum, testing for sensitivity to clarithromycin and should be quantitative rather than qualitative (i.e. minimum inhibitory and critical concentrations should be reported rather than statements of 'susceptible' or 'resistant'). This is in line with recommendations for the diagnosis and treatment of NTM pulmonary infections in the general population [42].

### 7.3.2 | Treatment

There are no published data of either sufficient quantity or quality to inform any standard recommendations for empirical or specific treatment of infection with minor species of NTM. The following discussion should therefore be considered informative but without any recommendations, other than regarding two general principles: phenotypic drug sensitivity testing should be performed on all NTM isolates deemed to be of clinical concern; and all cases should be referred to a suitably specialised centre or expert advice sought.

Drug regimens used to treat infection with NTM minor species are often empirical and almost always include a macrolide (clarithromycin or azithromycin) as the core agent, most frequently combined with ethambutol and a fluoroquinolone. Rifabutin is also frequently used. This approach recognises the fact that where drug sensitivity data have been collated, rates of resistance to isoniazid, streptomycin and rifampicin have been high. In some regions, considerable rates of resistance to macrolides and to ethambutol have also been reported [169, 202–205]. *M. abscessus* is particularly notable as an inherently drug-resistant organism [44]. It is important to note that the *M. abscessus* subspecies *abscessus* and *bolletii* are both known to have the potential for inducible resistance to macrolide antibiotics, due to the presence of the functional erythromycin ribosomal methylase (erm) gene *erm*41 (this gene is also present in *M. abscessus* subspecies *massiliense*, but in a non-functional form) [206]. Although macrolides may be useful for treating a proportion of *M. abscessus abscessus* infections, sequencing of the *erm*41 gene should be carried out in order to predict inducible loss of susceptibility to macrolide antibiotics, with particular caution in the case of any isolate demonstrating an initial mean inhibitory concentration of >8 μg/mL [207].

There are currently no systematic data to guide duration of therapy. Reported treatment lengths are highly variable and may even be lifelong in people with persistent immunosuppression, regardless of achieving sustained resolution of clinical and radiological features. Some clinicians advocate a minimum period of treatment from sterilisation of sputum samples (e.g. 12 months), although this is arbitrary and repeat sampling to demonstrate sterilisation is generally not realistic in extrapulmonary disease.

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## APPENDIX 1: LITERATURE SEARCHING AND PICO QUESTIONS

### Literature searching

The Medline, Embase and Cochrane Library databases were searched using the following terms: (HIV or AIDS) AND (atypical mycobacterial infections, *Mycobacterium avium* complex, *Mycobacterium avium intracellulare* or *Mycobacterium kansasii*). Searches were limited to English language papers published between 1980 and the date of the searches (June 2019).

Abstracts from selected conferences (Conference on Retroviruses and Opportunistic Infections, International AIDS Society/AIDS Conference, European AIDS Clinical Society, BHIVA, HIV Glasgow and Infectious Diseases Society of America) between January 2017 and June 2019 were also searched.

### PICO questions

1. Definition
   a. How is disseminated non-tuberculous mycobacteria (NTM) infection defined?
   b. How is localised NTM infection defined?

   c. What are the main differences in NTM infection between people living with HIV and the non-HIV population?
   d. Which are the most relevant types of NTM for people living with HIV?
2. Diagnosis
   a. What is the correct approach for diagnosis of NTM?
   b. Which investigations should be performed?
   c. What samples should be sent for testing?
   d. What microbiological tests should be performed?
   e. Does *in vitro* susceptibility predict resistance?
3. Management of patients
   a. Do patients need isolation?
   b. Which antimicrobials should be used in localised disease?
   c. Which antimicrobials should be used in disseminated disease?
   d. Which antimicrobials should be used in the case of macrolide resistance?
   e. What is the optimal length of treatment in localised disease?
   f. What is the optimal length of treatment in disseminated disease?
   g. Which tests should be performed during treatment monitoring?
   h. What is the correct approach to confirm cure/treatment failure/relapse?
4. Role of adjunctive therapy
   a. What is the role of antiretroviral therapy?
5. Prophylaxis
   a. Who should receive NTM prophylaxis?
   b. Which antimicrobials should be used for prophylaxis?
   c. What are the stopping criteria for prophylaxis?