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Management of opportunist mycobacterial infections: Joint Tuberculosis Committee guidelines 1999

Subcommittee of the Joint Tuberculosis Committee of the British Thoracic Society*

Guidelines have been produced for tuberculosis by the British Thoracic Society (BTS),[1 2] the American Thoracic Society (ATS),[3] the International Union Against Tuberculosis and Lung Disease,[4] and the World Health Organisation.[5] These, however, deal mainly with *Mycobacterium tuberculosis* complex infections (*M tuberculosis*, *M africanum*, and *M bovis*). With the exception of the ATS guidelines on non-tuberculous mycobacteria,[3] these do not address the opportunist mycobacteria (also called atypical mycobacteria, mycobacteria other than tuberculosis (MOTT), non-tuberculous mycobacteria (NTM), or environmental mycobacteria).

The number of isolates of such opportunist mycobacteria has been increasing,[6] both in HIV negative and HIV positive individuals. Because of the growing numbers of patients with disease due to infection by these mycobacteria, the wide range of species, the difficulties in both diagnosis and management, and in response to increasing requests for advice on management, the BTS Joint Tuberculosis Committee has reviewed the evidence on management of these infections. On the whole the evidence is not derived from controlled clinical trials as very few have been reported but, where possible, we have graded the evidence according to the criteria in table 1. Sections cover epidemiology, bacteriological aspects, diagnosis and treatment in adults and children, separated where appropriate into sections according to their HIV infection status.

Epidemiology

Opportunist mycobacteria can be found throughout the environment and can be isolated from soil, water (including tap water), dust, milk, and various animals and birds.[7–10] The significance of an isolate can only be established by considering the type of specimen from which the *Mycobacterium* was isolated, the number of isolates, the degree of growth, and the identity of the organism. In general, multiple isolates are needed from non-sterile sites to establish disease whereas one positive culture from a sterile site, particularly where there is supportive histopathology, is usually sufficient. The epidemiology may be complicated by the frequent isolation of opportunist mycobacteria from bronchoscopes and therefore from bronchial washings/lavages. The clinical presentation and any predisposing factors are also helpful. Patients with pre-existing lung disease or deficient immune systems seem more prone to these infections than those without such predisposing conditions. Good communication between the laboratory and clinician is essential. Additional specimens should be taken if unusual opportunist mycobacteria are identified at sites that do not appear to fit the clinical picture. Clinicians should ensure that adequate specimens are sent and that the laboratory receives clear information regarding the site and type of specimen, the patient's age and clinical details, including whether the patient is immunocompromised.

Table 1 Gradings of recommendations

Grade A	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
Grade B	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation
Grade C	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities, but indicates absence of directly applicable studies of good quality

These organisms are low grade pathogens in humans and cross infection is very rare. Several epidemiological studies employing DNA finger printing techniques, serology, and skin test antigens have established that person-to-person transmission is very unusual even with smear positive sputum.[11–13] It is not therefore considered necessary to notify patients with infection, nor is it necessary to trace contacts.[14] If a patient has been notified as a case of tuberculosis on the basis of a positive smear and/or chest radiographic appearances but later is found on culture to have an opportunist mycobacterial organism, the patient should be de-notified and any contact tracing or chemoprophylaxis for tuberculosis discontinued. The patient's treatment should be altered to the regimen recommended for that opportunist *Mycobacterium*.

In the UK a small number of reported mycobacterial infections are caused by opportunist species but there are large geographical variations, both in absolute numbers and in the proportion of the different species.[15] The numbers of species recognised have increased with the development of new culture techniques and molecular sequencing analysis but human disease is primarily associated with a limited number of species (table 2). In immunocompetent patients *M kansasii* is the most common opportunist mycobacterial pathogen in England and Wales whilst *M malmoense* is the most common in Scotland. *M xenopi* predominates in the south east of England (37% of opportunist mycobacterial infections compared with 28% due to *M kansasii*, 20%

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Table 2 Principal opportunist Mycobacterium species causing human disease

Disease site	*Opportunist species*
Pulmonary	*M avium* complex
	M kansasii
	M xenopi
	M malmoense
	M abscessus
	M fortuitum
	M celatum
	M asiaticum
	M sulgai
Lymph node	*M avium* complex
	M malmoense
	M scrofulaceum
	M genavense
Cutaneous/musculoskeletal	*M marinum*
	M ulcerans
	M fortuitum
	M abscessus
	M chelonae
	M avium complex
	M kansasii
	M malmoense
	M terrae
Disseminated	*M avium* complex
	M kansasii
	M genavense
	M chelonae
	M abscessus
	M haemophilum
	M scrofulaceum
	M celatum
	M simiae
	M malmoense

due to *M avium* complex (MAC), and 8% to *M fortuitum* or *M chelonae*).[16]

Pulmonary disease, lymphadenitis, and disseminated infection are the commonest and most important clinical problems but infection and disease do occur at other sites, such as the soft tissues, bone, joints, and genitourinary tract.

In patients with HIV/AIDS MAC infection is particularly common and this phenomenon has altered the patterns of disease seen in the UK. MAC is responsible for over 90% of the opportunist mycobacterial infections in patients with HIV/AIDS (F Drobniewski, personal communication).

Diagnostic methods

Primary samples from non-sterile sites are decontaminated using the same methods as applied to samples taken for tuberculosis. Staining is with Ziehl-Neelsen or Kinyoun carbol fuchsin based procedures or auramine-phenol fluorochrome methods to detect mycobacteria. No conclusions can be made on the identity of mycobacteria from the microscopic appearance in primary samples. High performance liquid chromatography (HPLC) and molecular DNA methodology can be applied to primary samples[17] but, in practice, identification of cultured opportunist mycobacteria remains the cornerstone of diagnosis.

Samples should be inoculated onto at least one solid medium (Lowenstein-Jensen (LJ) or Middlebrook 7H10 and 7H11) and into a liquid culture system (BACTEC 460, MGIT, MB9000, MB BacT, ESP).[18 19] The latter systems permit more rapid culture and isolation of a greater range of species than do the use of solid media alone, but solid culture permits quantification of the isolated *Mycobacterium*. Some species do not grow without modification to the growth medium. Scanty growth against an inappropriate clinical background should raise suspicions that the isolated organism is merely an environmental contaminant. Opportunist mycobacteria are identified by the pattern of pigmentation, growth characteristics, microscopic appearance, and biochemical reactions. More rapid discriminating systems are being developed—for example, DNA probes, HPLC, polymerase chain reaction restriction enzyme analysis (PRA), and 16S rRNA gene sequence analysis.[17 20–24] Rapid identification of cultures using species-specific probes is currently limited to MAC, *M kansasii*, and *M gordonae*.

SKIN TESTING

Differential skin testing is not reliable enough for accurate diagnosis[25–27] and is not recommended. **(B)**

Opportunistic mycobacterial infections in HIV negative patients

CLINICAL FEATURES

Pulmonary disease

M kansasii, MAC, *M malmoense*, and *M xenopi* are the species which most often cause lung disease. Most patients are middle aged to elderly men, over half of whom usually have chronic bronchitis and emphysema, old healed tuberculosis, or both.[28–31] The illness presents acutely or subacutely in a way that is clinically and radiologically very like that caused by infection with *M tuberculosis*, although some patients may be asymptomatic. Not only are the appearances on the chest radiograph indistinguishable from those caused by *M tuberculosis*, but they are also indistinguishable between the various opportunist mycobacterial species. Cavitation occurs in 70–90%.[29 31–33] Pulmonary disease is diagnosed when positive cultures develop from specimens of sputum obtained at least seven days apart in a patient whose chest radiograph suggests mycobacterial infection and who may or may not present with symptoms and signs. In patients with more chronic presentation and a radiograph which is difficult to interpret, the diagnosis of disease, as opposed to colonisation of previously damaged lung, may be difficult to make. Indeed, sometimes after a period of colonisation, disease may develop.[34]

Lymphadenitis

Predominantly, this is a disease of children between the ages of one and five years, presenting most frequently in the cervical lymph nodes. Often just one node is involved which may be "hot" or "cold". There is little systemic upset, the glands usually being painless and non-tender.[35 36] The chest radiograph is normal. The organisms are usually MAC or *M malmoense*. A diagnosis is made by complete resection of the involved gland(s) and culture of the specimen. Histologically the appearances are the same as those caused by *M tuberculosis*. Accurate diagnosis and proper treatment will be expedited by close co-operation between chest physicians, paediatricians, and

Table 3 Recommended regimens for HIV negative patients with disease due to opportunist mycobacteria

	Regimen	*Duration*
Pulmonary disease:		
M kansasii	Rifampicin 450 mg orally o.m. if <50 kg; 600 mg orally if ⩾50 kg Ethambutol 15 mg/ kg orally o.m.	9 months
M avium complex (MAC)	Rifampicin (dose as above)	2 years
M malmoense	Ethambutol (dose as above)	
M xenopi	(± isoniazid 300 mg orally o.m.)	
Others	See text	See text
Lymph node:		
M kansasii	Excision. If recurrence, further excision + rifampicin and ethambutol	2 years
M malmoense	daily (doses as above)	
M xenopi		
MAC	Excision. If recurrence, further excision + rifampicin and ethambutol (doses as above) and clarithromycin (500 mg orally b.d.)	2 years
Others	See text	See text
Intolerance to rifampicin or ethambutol	Substitute clarithromycin and/or ciprofloxacin	

other specialists including ear, nose and throat surgeons and microbiologists. In adults *M tuberculosis* is a more likely cause of lymphadenitis.

Disease at other extrapulmonary sites

M fortuitum or *M chelonae* tend to infect the skin or soft tissues after penetrating trauma or surgery, with recurrent abscess or fistula formation. *M marinum* infection may occur following trauma to the skin in contaminated swimming pools or aquaria ("swimming pool" or "fish tank granuloma").[37] *M ulcerans* may cause chronic, indolent necrotic skin ulcers known as "Buruli ulcers", but this condition is only rarely seen outside Africa.[38] Infections of bone, joints, and the genitourinary tract are rare.

TREATMENT

The lack of consensus here reflects the absence of large clinical trials designed to assess various regimens and, until now, treatment has been derived from the results of small, retrospective or, occasionally, prospective studies which are often not comparable. Inappropriate extension of the principles derived from the treatment of *Mycobacterium* tuberculosis into the treatment of opportunist mycobacterial infections has been a further cause of confusion. In general, results from standard tests are of little or no value in predicting clinical efficacy in infections by opportunist mycobacteria.[39] The exception is sensitivity testing for rifampicin and ethambutol in *M kansasii* infection (and clarithromycin sensitivity testing in HIV positive patients). Synergy between drugs to which resistance may have been reported in vitro on single agent testing may be of importance in vivo.[40 41] It is preferable that patients with these diseases be managed by chest physicians, if only because they are more likely to be familiar with using antimycobacterial drugs and with their unwanted effects.

M kansasii pulmonary disease

The retrospective study by Banks *et al* emphasised the importance of rifampicin and ethambutol in the treatment of *M kansasii*. In a series of 30 patients treated for 3–24 months (mean 15 months) there was 100% cure without any relapses during follow up for a mean of five years.[42] The BTS has conducted a large prospective study of nine months' treatment with rifampicin and ethambutol in 175 patients. Only one failed to convert to negative cultures by the end of treatment, a patient who admitted poor compliance. Of 154 patients entering the follow up period after chemotherapy, 15 (10%) developed positive cultures in the subsequent 51 months. The relapse rate was no different between those who had received isoniazid initially and those who had not.[29] In eight patients a factor that could have influenced relapse was identified—for example, lack of compliance, malnourishment, corticosteroid treatment, severe bronchiectasis, or the development of carcinoma. In three other patients the new positive cultures were accompanied by fresh changes in the radiograph on the side other than that originally involved, or in a lobe different from the lobe originally involved. In the only other prospective study in the literature 40 patients were given rifampicin, ethambutol and isoniazid for 12 months and during 3–5 years of follow up one patient (2.5%) relapsed.[43] In Czechoslovakia a retrospective study of 471 patients treated for 9–12 months with various antimycobacterial regimens revealed a relapse rate of 8% during 1–7 years of follow up after chemotherapy.[30] Other small retrospective studies testify to the efficacy of rifampicin and ethambutol.[44–46]

Treatment with rifampicin and ethambutol for nine months can be recommended as sufficient for most patients (table 3) but, for those with obviously compromised immune defences, it would be wise to continue treatment for 15–24 months or until the sputum has been negative for 12 months. **(B)**

In those suspected of non-compliance with chemotherapy, follow up should be indefinite and any relapses re-treated with ethambutol and rifampicin for 15–24 months. **(B)** Prothionamide (1 g/day orally) and streptomycin (0.75–1 g/day intramuscularly) should be added to the regimen for those who fail to respond to the combination of ethambutol and rifampicin. **(C)**

Macrolides are active in vitro against *M kansasii* but their place in treatment remains to be assessed by clinical trials, as does the place of fluoroquinolones.

M kansasii extrapulmonary disease

In England and Wales, between 1982 and 1994, only 9% of 759 *M kansasii* infections were extrapulmonary.[14] Lymph node infection,

usually a disease of young children, is best treated by excision of the affected nodes.[35 47] **(C)**

Aspiration of the node, incision, or drainage should be avoided because of the possibility of leaving a discharging sinus and ugly scar. Chemotherapy has sometimes been used to debulk the lesion so that complete excision can be performed. Recurrence of disease should be treated by further excision followed by chemotherapy with rifampicin and ethambutol for 9–24 months. **(C)**

There are insufficient data about duration of treatment for infection at sites other than superficial lymph nodes; in the first instance it would seem sensible to give ethambutol and rifampicin for nine months and to add prothionamide and streptomycin and/or a macrolide if the condition is not responding. **(C)**

M avium complex (MAC) pulmonary disease

Many authors report that results of treatment are poor, with a response rate of about 50% and 20% relapses.[48 49] In a retrospective review Hunter *et al* noted that symptomatic patients who were not treated were likely to die, whilst asymptomatic patients might survive without treatment but some clearly went on to develop aggressive disease. In that series the best results were reported with triple therapy with either rifampicin, streptomycin and isoniazid or with rifampicin, ethambutol and isoniazid for 9–24 months. Satisfactory clinical, radiological, and bacteriological responses were noted in 84% of cases but 14% relapsed within a year of treatment. When second or third line drugs were used, or regimens with four or more drugs, the results were poor, most patients experiencing toxicity and becoming non-compliant with treatment.[50]

Based on the results of in vitro data on synergy,[40 41] the BTS has recently conducted a prospective comparison of a regimen containing ethambutol and rifampicin with one containing ethambutol, rifampicin and isoniazid, both regimens being given for 24 months. The results show that 28% either failed to convert to culture negative by the end of the treatment period or relapsed during the three year follow up period.[51] With the triple regimen, although there tended to be fewer failures and relapses, there also tended to be more deaths attributed to the MAC infection. In patients who fail/relapse the alternatives are to continue treatment indefinitely or to add one or more of ciprofloxacin (750 mg orally twice daily), clarithromycin (500 mg orally twice daily), or streptomycin (0.75–1 g intramuscularly once daily) to the regimen until the culture has been negative for a period of 12 months. As yet, however, there is no proof from clinical trials that such addition(s) to the regimen would confer any added benefit over the regimen of rifampicin and ethambutol. In those who are fit enough for surgery and where the disease is unilateral, resection and continuation of treatment is an option.[52 53] There is no evidence from clinical trials that rifabutin is superior to rifampicin as part of these regimens. The current study by the BTS should provide information about the usefulness of clarithromycin and ciprofloxacin as adjuncts to rifampicin and ethambutol, as well as the value of immunotherapy with *M vaccae*. In the meantime, first line treatment should be with rifampicin and ethambutol (in vitro sensitivity results notwithstanding) for 24 months, plus or minus isoniazid (table 3). **(B)**

M avium complex (MAC) extrapulmonary disease

This occurs predominantly in the cervical lymph nodes of children. The treatment of choice is complete excision of the affected nodes.[54 55] Antimycobacterial chemotherapy with rifampicin, ethambutol and clarithromycin for up to two years should be considered in those patients where disease recurs or where surgical excision is incomplete or impossible because of involvement or proximity of vital structures, or to debulk in order to permit excision (table 3). Properly conducted clinical trials are needed to establish optimal regimens. In sites other than lymph nodes we recommend chemotherapy for 18–24 months. **(C)**

M malmoense pulmonary disease

Again the important drugs appear to be ethambutol and rifampicin. In two retrospective studies it was noted that patients treated for 18–24 months with regimens which included those drugs did better than those in whom other regimens or shorter durations of treatment were used.[56 57] The addition of second or third line drugs to the regimen or the use of four or five drug regimens were associated with poor tolerance and poor results. In those not responding satisfactorily to chemotherapy but fit enough for surgery, resection of the affected lobe(s) is an option if disease is unilateral. Chemotherapy should be continued after surgery for at least 18 months. In the recently concluded BTS trial 10% of patients remained positive on culture or relapsed after two years of treatment with rifampicin and ethambutol or these drugs plus isoniazid.[51] The current BTS trial aims to assess the places of ciprofloxacin, clarithromycin, and *M vaccae* in the treatment of this infection, when added to the basic regimen of rifampicin and ethambutol. Meanwhile, treatment for 24 months with rifampicin and ethambutol is recommended as offering the best balance between cure and unwanted effects (table 3). **(B)**

M malmoense extrapulmonary disease

Superficial lymph node infection is the commonest form and is usually a disease of children.[58] The treatment of these infections, and infections of other sites, is the same as the treatment for those conditions caused by *M kansasii* or MAC (see above and table 3). **(C)**

M xenopi pulmonary disease

These infections pose an even greater challenge than do infections with MAC or *M malmoense*. Disease may progress on treatment, even if the regimens include ethionamide and cycloserine

on the basis of standard in vitro sensitivity tests. When these drugs are included, toxicity and poor compliance contribute to poor outcome.[59 60] Surgery is an option for very few because of co-existing lung or cardiac conditions. In the recent BTS trial 10% failed to convert to culture negative or relapsed after two years of treatment with rifampicin and ethambutol or with rifampicin, ethambutol, and isoniazid.[51] The overall death rate within five years was 55%, 7% due to the *M xenopi* infection (trend to more deaths with the triple regimen than the two drug regimen), rates considerably above those seen with MAC or *M malmoense*. The places of ciprofloxacin, clarithromycin, and immunotherapy with *M vaccae* are under study in the current BTS trial. Pending these results the recommended regimen is treatment for two years with ethambutol and rifampicin, using surgery for those who fail to respond and are fit enough for the operation (table 3). **(B)**

M xenopi extrapulmonary disease
This has rarely been described and the same considerations would apply as do to MAC, *M malmoense*, and *M kansasii.* **(C)**

Pulmonary disease due to rapidly growing mycobacteria (M chelonae, M fortuitum, M abscessus, M gordonae) and other species (M simiae, M szulgai, M ulcerans, M genavense, M haemophilum)
These infections are rare and difficult to treat although standard in vitro susceptibility testing appears to be of some value in determining regimens in this group.[61–64] In the absence of clinical trials and in view of the paucity of retrospective series containing any more than a single patient or 2–3 patients, it is difficult to give guidance. If surgery is possible it should be employed. Regimens should probably include rifampicin (450 mg if <50 kg, 600 mg if ⩾50 kg), ethambutol (15 mg/kg), and clarithromycin (500 mg twice daily), preferably all taken together orally each morning. Quinolones, sulphonamides, amikacin, cefoxitin, and imipenem may have a place in treatment.[61–72] Cure may not be attainable. **(C)**

Extrapulmonary disease due to rapidly growing mycobacteria (M chelonae, M fortuitum, M abscessus, M gordonae) and other species (M simiae, M szulgai, M ulcerans, M genavense, M haemophilum)
Treatment of wound infection with *M fortuitum* or *M chelonae* should be by surgical debridement followed by ciprofloxacin (750 mg orally twice daily) and an aminoglycoside or imipenem.[64 73–75] Some physicians would include clarithromycin (500 mg orally twice daily) when treating these infections.[76] *M marinum* skin infection may heal spontaneously but successful treatment has been reported with cotrimoxazole,[77] tetracycline,[78] and the combination of rifampicin and ethambutol in standard doses.[79] With *M ulcerans* wide excision with skin grafting is the treatment of choice,[80] although a regimen of rifampicin, ethambutol, and clarithromycin in standard doses may be effective in early disease.[81]

It is not certain how long chemotherapy should be continued for these infections as there is no evidence from controlled clinical trials. If the response to initial treatment for six months is anything less than optimal, then prolonging chemotherapy for up to two years would seem sensible. **(C)**

Opportunistic mycobacterial infections in HIV positive/AIDS patients

CLINICAL FEATURES

Pulmonary disease
Disease confined to the lungs is rare in HIV positive patients, accounting for less than 5% of the opportunist mycobacterial infections in this group. Symptoms are very like those seen in HIV negative patients but haemoptysis is less common. The chest radiograph shows diffuse interstitial or reticulonodular infiltrates in about half of cases, whereas alveolar infiltrates occur in 20%. Apical scarring or upper lobe involvement occurs in less than 10%. Cavitatory disease is unusual, occurring in less than 5%.[82 83]

A single isolate from sputum may represent colonisation but repeated isolates in patients with symptoms and/or radiographic changes warrant treatment.

Lymphadenitis
This is seen occasionally without evidence of disseminated disease and can be associated with cutaneous lesions.[84] Some patients present with pyrexia of unknown origin. Until the diagnosis is confirmed by culture, such lymphadenitis should be regarded as being due to *M tuberculosis* and treated accordingly.[2]

Disease at other extrapulmonary sites
Progressive immunodeficiency appears to be the single most significant risk factor for disseminated mycobacterial disease, which is mostly caused by MAC.[85 86] However, the incidence of disseminated disease is decreasing in most centres because of the use of highly active antiretroviral therapy (HAART) which restores some immunocompetence, and the use of prophylactic antimycobacterial drug(s). On starting HAART some patients who are on treatment for bacteraemic MAC may transiently develop an immune phenomenon of fever, new lymphadenopathy, or worsening of existing lymph node and skin lesions. This is not usually due to relapse of the disease. If these patients are distressed by their symptoms a short course of corticosteroids is helpful.

TREATMENT
Restoring as much immunocompetence as possible with combinations of antiretroviral agents is probably as important, if not more so, than antimycobacterial therapy. As with HIV negative patients, the relationship between the results of sensitivity tests and clinical response is different from the relationship in *M tuberculosis* infections.[87] The choice of antimycobacterial regimens is further complicated by

Table 4 Recommended regimens for HIV positive patients with disease due to opportunist mycobacteria

	Regimen	*Duration*
Pulmonary or disseminated disease:		
M avium complex (MAC) *M kansasii* *M malmoense* *M xenopi*	Rifampicin 450 or 600 mg orally once daily (or rifabutin 300 mg once daily), ethambutol 15 mg per kg orally once daily, and clarithromycin 500 mg orally b.d.	Lifelong
Prophylaxis against MAC:		
1st choice	Azithromycin 1200 mg orally weekly	Indefinitely
2nd choice	Clarithromycin 500 mg orally b.d.	Indefinitely
3rd choice	Azithromycin 1200 mg orally weekly + Rifabutin 300 mg orally once daily.	Indefinitely
Drug interactions in HIV positive patients:		
Rifabutin + clarithromycin	Uveitis	
Rifabutin + fluconazole	Greatly reduces fluconazole levels	
Rifampicin, Rifabutin } + protease inhibitors	Decrease in serum level of protease inhibitors, increase in serum level of rifampicin and rifabutin	

interactions between macrolides, rifamycins, and protease inhibitors.

M kansasii pulmonary disease

M kansasii usually appears late in the course of HIV infection when patients are often profoundly immunosuppressed. About half of the patients have disease localised to the lungs. Untreated pulmonary disease can be rapidly fatal, eight of 17 patients dying within three months of diagnosis. Nine patients who were given antimycobacterial chemotherapy improved clinically and radiologically and converted bacteriologically.[88]

Pending further evidence from clinical trials, it would appear sensible to give such patients rifampicin and ethambutol for two years (table 3) or until the sputum has been negative on culture for 12 months. In patients who are on HAART there is likely to be a problem with drug interaction with protease inhibitors. One possible approach might be to substitute rifabutin (300 mg orally once daily) for rifampicin if indinavir, amprenavir, or nelfinavir is chosen as protease inhibitor but no trials have been conducted using rifabutin. Alternatively, anti-retroviral regimens without protease inhibitors can be considered.[89] The places of macrolides and fluoroquinolones remain to be established. **(C)**

M kansasii disseminated disease

M kansasii is the second most frequent cause of disseminated mycobacteriosis in AIDS patients, accounting for 3%.[90] Lungs, lymph nodes, bones, joints, and skin can be affected, with variable appearances on the chest radiograph. Even in the face of advanced immunosuppression, eight of 11 patients with disseminated disease survived at least three months on rifampicin and ethambutol, some also receiving isoniazid.[91] In the present state of knowledge, treatment should be with rifampicin, ethambutol, and clarithromycin (table 4), possibly also with isoniazid for as long as the patient lives. **(C)**

Again, the places of macrolides and quinolones need to be established. Effective restoration of the immune system with HAART may allow discontinuation of chemotherapy.

MAC pulmonary disease

A number of drugs has been tried but few of the trials have been properly designed and conducted.[92–94] Adverse effects leading to premature discontinuation of treatment are more common in the HIV positive population and occur more frequently as the number of drugs used in combinations is increased.[94 95] Most clinicians would continue life long therapy because discontinuation often results in recurrence of disease and bacteraemia.[96] Going on the available evidence, treatment should consist of rifampicin, ethambutol, and clarithromycin or azithromycin (500 mg orally once daily) with the same caveats about rifamycins/protease inhibitors as discussed earlier (table 4). Ciprofloxacin (750 mg orally twice daily) or another quinolone, or even amikacin (15 mg/kg daily in two divided doses, intravenously or intramuscularly), may be added for patients who are intolerant of other drugs or fail to respond to the initial regimen. **(C)**

MAC disseminated disease

Bacteraemia occurs in over 95% of patients with dissemination, in contrast to *M tuberculosis* infection when blood cultures are seldom positive. The literature on treatment is characterised by a lack of properly designed, prospective, controlled clinical trials. Only three have been placebo controlled and double blind. Macrolides and ethambutol are important in treatment and the addition of rifabutin may confer added benefit. There have been no head to head comparisons of the cheaper drug, rifampicin, with rifabutin. Mortality is higher when clofazamine is used and the place of the quinolones remains to be defined.[97 98] Pending publication of the results of ongoing studies, treatment should be given as for pulmonary disease (table 4) and continued indefinitely unless there is confidence that the immune system has been restored by HAART. **(C)**

M malmoense pulmonary disease

M malmoense is rarely isolated from AIDS patients,[99 100] occurring at a late stage when the CD4 count is below 50 cells/mm^3. In the present state of knowledge treatment should be with rifampicin, ethambutol, and clarithromycin (table 4), possibly also with isoniazid (300 mg orally once daily), for as long as the patient lives. **(C)**

The places of macrolides and quinolones remain to be established. Surgery is unlikely to be an option in these severely ill patients.

M xenopi pulmonary disease

When *M xenopi* is cultured it is usually one among other pathogens such as *Pneumocystis* and/or *M tuberculosis*.[101] There is no evidence in HIV/AIDS patients on which to base treatment recommendations; the regimen shown in table 4 is suggested. **(C)**

Pulmonary disease with rapidly growing mycobacteria (M chelonae, M fortuitum, M abscessus, M gordonae)

Infection by these organisms usually leads to symptoms and signs much like those in HIV negative patients, but in a more florid form. In the present state of knowledge it seems fairest to say that treatment should be as given for HIV negative patients. **(C)**

PROPHYLAXIS FOR DISSEMINATED MAC

There is no general agreement about when prophylaxis should be used. Two randomised placebo controlled trials of rifabutin as prophylaxis in the USA and Canada have shown a significant reduction in the incidence of MAC bacteraemia in patients with CD4 counts of <200 cells/mm^3, with a trend towards increased survival.[102] Side effects led to discontinuation of treatment in 16% of the active group compared with 8% in the placebo group. In a double blind, placebo controlled trial clarithromycin more than halved the recurrence of bacteraemia in the treatment group (6% versus 16% with placebo) and there was also benefit to survival (hazard ratio 0.75, 95% confidence interval 0.58 to 0.97). Adverse events occurred in one third of the patients in both groups. Adding rifabutin to clarithromycin did not improve efficacy.[103] In terms of efficacy the combination of weekly azithromycin and daily rifabutin did better than either drug alone, but dose limiting adverse events were more common in the combination group.[104]

In general terms monotherapy with rifamycins should be avoided in prophylaxis because of the possibility of the emergence of resistance to this class of drugs among those co-infected with *M tuberculosis*.[105] Macrolide resistance is less relevant to tuberculosis. Care should also be taken because of the interactions between rifamycins, macrolides, and antiretroviral treatment, especially protease inhibitors.[89]

If prophylaxis is to be given to patients with CD4 counts which remain <50 cells/mm^3, weekly azithromycin appears to be the most cost effective option (table 4). **(C)**

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