

# 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),<sup>1,2</sup> the American Thoracic Society (ATS),<sup>3</sup> the International Union Against Tuberculosis and Lung Disease,<sup>4</sup> and the World Health Organisation.<sup>5</sup> 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,<sup>3</sup> 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,<sup>6</sup> 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.<sup>7-10</sup> 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.

These organisms are low grade pathogens in humans and cross infection is very rare. Several epidemiological studies employing DNA fingerprinting techniques, serology, and skin test antigens have established that person-to-person transmission is very unusual even with smear positive sputum.<sup>11-13</sup> It is not therefore considered necessary to notify patients with infection, nor is it necessary to trace contacts.<sup>14</sup> 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.<sup>15</sup> 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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Received 10 May 1999  
Returned to author  
23 July 1999  
Revised manuscript received  
14 October 1999  
Accepted for publication  
22 November 1999

Table 1 Gratings 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

Table 2 Principal opportunist *Mycobacterium* species causing human disease

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

due to *M. avium* complex (MAC), and 8% to *M. fortuitum* or *M. chelonae*).<sup>16</sup>

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 Drobniowski, 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<sup>17</sup> 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).<sup>18, 19</sup> 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 modi-

fication 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.<sup>17, 20–24</sup> Rapid identification of cultures using species-specific probes is currently limited to MAC, *M. kansasii*, and *M. goodii*.

### SKIN TESTING

Differential skin testing is not reliable enough for accurate diagnosis<sup>25–27</sup> 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.<sup>28–31</sup> 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%.<sup>29, 31–33</sup> 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.<sup>34</sup>

#### 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.<sup>35, 36</sup> 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:		
<i>M. kansasii</i>	Rifampicin 450 mg orally o.m. if <50 kg; 600 mg orally if ≥ 50 kg	9 months
	Ethambutol 15 mg/kg orally o.m.	
<i>M. avium</i> complex (MAC)	Rifampicin (dose as above)	2 years
<i>M. malmoense</i>	Ethambutol (dose as above)	
<i>M. xenopi</i>	(± isoniazid 300 mg orally o.m.)	
Others	See text	See text
Lymph node:		
<i>M. kansasii</i>	Excision. If recurrence, further excision + rifampicin and ethambutol	2 years
<i>M. malmoense</i>	daily (doses as above)	
<i>M. xenopi</i>		
MAC	Excision. If recurrence, further excision + rifampicin and ethambutol	2 years
	(doses as above) and clarithromycin (500 mg orally b.d.)	
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").<sup>37</sup> *M. ulcerans* may cause chronic, indolent necrotic skin ulcers known as "Buruli ulcers", but this condition is only rarely seen outside Africa.<sup>38</sup> 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.<sup>39</sup> 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.<sup>40-41</sup> 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.<sup>42</sup> 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.<sup>29</sup> 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.<sup>43</sup> 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.<sup>30</sup> Other small retrospective studies testify to the efficacy of rifampicin and ethambutol.<sup>44-46</sup>

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.<sup>14</sup> Lymph node infection,

usually a disease of young children, is best treated by excision of the affected nodes.<sup>35–47</sup>

### (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.<sup>48–49</sup> 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.<sup>50</sup>

Based on the results of *in vitro* data on synergy,<sup>40–41</sup> 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.<sup>51</sup> 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.<sup>52–53</sup> There is no evidence from clinical trials that rifabutin is superior to rifampicin as part of these regimens. The cur-

rent 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.<sup>54–55</sup> 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.<sup>56–57</sup> 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.<sup>51</sup> 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.<sup>58</sup> 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.<sup>59-60</sup> 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.<sup>51</sup> 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.<sup>61-64</sup> 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.<sup>61-72</sup> 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.<sup>64-73-75</sup> Some physicians would include clarithromycin (500 mg orally twice daily) when treating these infections.<sup>76</sup> *M marinum* skin infection may heal spontaneously but successful treatment has been reported with cotrimoxazole,<sup>77</sup> tetracycline,<sup>78</sup> and the combination of rifampicin and ethambutol in standard doses.<sup>79</sup> With *M ulcerans* wide excision with skin grafting is the treatment of choice,<sup>80</sup> although a regimen of rifampicin, ethambutol,

and clarithromycin in standard doses may be effective in early disease.<sup>81</sup>

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%. Cavitory disease is unusual, occurring in less than 5%.<sup>82-83</sup>

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.<sup>84</sup> 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.<sup>2</sup>

##### *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.<sup>85-86</sup> 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.<sup>87</sup> 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: <i>M. avium</i> complex (MAC) <i>M. kansasii</i> <i>M. malmoense</i> <i>M. xenopi</i>	Lifelong
Prophylaxis against MAC: 1st choice 2nd choice 3rd choice	Indefinitely Indefinitely Indefinitely
Drug interactions in HIV positive patients: Rifabutin + clarithromycin Rifabutin + fluconazole Rifampicin } + protease Rifabutin } inhibitors	Uveitis Greatly reduces fluconazole levels 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.<sup>88</sup>

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.<sup>89</sup> 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%.<sup>90</sup> 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.<sup>91</sup> 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.<sup>92-94</sup> 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.<sup>94-95</sup> Most clinicians would continue life long therapy because discontinuation often results in recurrence of disease and bacteraemia.<sup>96</sup> 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.<sup>97-98</sup> 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,<sup>99-100</sup> occurring at a late stage when the CD4 count is below 50 cells/mm<sup>3</sup>. 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*.<sup>101</sup> 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<sup>3</sup>, with a trend towards increased survival.<sup>102</sup> 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.<sup>103</sup> 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.<sup>104</sup>

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*.<sup>105</sup> 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.<sup>89</sup>

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

The Subcommittee is grateful to Mrs Elizabeth Lyons and Mrs Diane Wyatt for typing the manuscript.

- 1 Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations of the Joint Tuberculosis Committee of the British Thoracic Society. *Thorax* 1990;45:403-8.
- 2 Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations. *Thorax* 1998;53:536-48.
- 3 American Thoracic Society. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med* 1994;149:1359-74.
- 4 International Union Against Tuberculosis and Lung Disease. Antituberculosis regimens of chemotherapy: recommendation from the committee on treatment of IUATLD. *Bull Int Union Tuberc Lung Dis* 1988;63:60-4.

- 5 World Health Organisation Tuberculosis Unit. Division of Communicable Disease *Guidelines for tuberculosis treatment in adults and children in national treatment programmes*. WHO/TB/91. Geneva: World Health Organisation, 1991: 1-61.
- 6 Mycobnet data.
- 7 Chapman JS. The ecology of the atypical mycobacteria. *Arch Environ Health* 1971;22:41-6.
- 8 Chapman JS, Bernard JS, Speight M. Isolation of bacteria from raw milk. *Am Rev Respir Dis* 1965;91:351-5.
- 9 Marks J, Jenkins PA. The opportunist mycobacteria - 20 year retrospect. *Postgrad Med J* 1971;47:705-9.
- 10 McSwiggan DA, Collins CH. The isolation of *M kansasii* and *M xenopi* from water systems. *Tubercle* 1974;55:291-7.
- 11 Penny ME, Cole RB, Grey J. Two cases of *Mycobacterium kansasii* infection occurring in the same household. *Tubercle* 1982;63:129-30.
- 12 von Reyn CF, Maslow AN, Barber TW, et al. Persistent colonisation of potable water as a source of *Mycobacterium avium* infection in AIDS. *Lancet* 1994;343:1137-41.
- 13 Meissner G, Anz W. Sources of *Mycobacterium avium* complex infection resulting in human disease. *Am Rev Respir Dis* 1997;116:1057-64.
- 14 Ormerod LP, Watson JM, Pozniak A, et al. Notification of tuberculosis: an updated code of practice for England and Wales. *J R Coll Physicians* 1997;31:299-203.
- 15 Lambden K, Watson JM, Kerner G, et al. Opportunist mycobacteria in England and Wales: 1982-1994. *CDR Review* 1996;11:147-51.
- 16 Grange JM, Yates MD. Infections caused by opportunist mycobacteria: a review. *J R Soc Med* 1986;79:226-9.
- 17 Jost KC, Dunbar DF, Barth SS, et al. Identification of *Mycobacterium tuberculosis* and *M avium* complex directly from smear-positive sputum specimens and BACTEC12B cultures by high performance liquid chromatography with fluorescent detection and computer-driven pattern recognition models. *J Clin Microbiol* 1995;33:1270-7.
- 18 Heifets LB. Quantitative cultures and drug susceptibility testing of *Mycobacterium avium* clinical isolates before and during antimicrobial therapy. *Res Microbiol (Paris)* 1994; 145:188-96.
- 19 Wilson ML, Stone BL, Hildred MV, et al. Comparison of recovery rates for mycobacteria from BACTEC 128 vials, Middlebrook 7H11-selected 7H11 bi-plates, and Lowenstein-Jensen slants in a public health microbiology laboratory. *J Clin Microbiol* 1995;33:2516-8.
- 20 Drobniński FA. Mycobacterial speciation. In: Parish T, Stoker N, eds. *Methods in molecular biology*. Oxford: Humana Press, 1998;101:323-47.
- 21 Butler WR, Ahearn DG, Kilburn JO. High performance liquid chromatography of mycolic acids as a tool in the identification of *Corynebacterium*, *Nocardia*, *Rhodococcus* and *Mycobacterium* species. *J Clin Microbiol* 1986;23:182-5.
- 22 Woods OL, Fish G, Plaunt M, et al. Clinical evaluation of Difco ESP Culture System II for growth and detection of mycobacteria. *J Clin Microbiol* 1997; 35:121-4.
- 23 Witebsky FG, Kruczak-Filipov P. Identification of mycobacteria by conventional methods. In: Heifets L, ed. *Clinics in laboratory medicine: clinical microbiology*. 1996;16:56-601.
- 24 Roberts GD, Bottger EC, Stockman L. Methods for the rapid identification of mycobacterial species. In: Heifets L, ed. *Clinics in laboratory medicine: clinical microbiology*. 1996;16:603-15.
- 25 Del Beccaro MA, Mendelman PM, Noland C. Diagnostic usefulness of mycobacterial skin test antigens in childhood lymphadenitis. *Paediatr Infect Dis J* 1989;8:206-10.
- 26 Huebner RE, Schein MF, Cauthen GM, et al. Usefulness of skin testing with mycobacterial antigens in children with cervical lymphadenopathy. *Paediatr Infect Dis J* 1992;11: 450-6.
- 27 von Reyn CF, Green PA, McCormick D, et al. Dual skin testing with *Mycobacterium avium* sensitin and purified protein derivative: an open study of patients with *M avium* complex infection or tuberculosis. *Clin Infect Dis* 1994;19: 15-20.
- 28 Campbell IA, Jenkins PA. Opportunist mycobacterial infections. In: Brewis RAL, Corrin B, Geddes DM, Gibson GJ, eds. *Respiratory medicine*. London: WB Saunders, 1995: 840-7.
- 29 British Thoracic Society. *Mycobacterium kansasii* pulmonary infection: a prospective study of the results of nine months of treatment with rifampicin and ethambutol. *Thorax* 1994; 49:442-5.
- 30 Kaustova J, Chmelik M, Ettlova D, et al. Disease due to *Mycobacterium kansasii* in the Czech Republic 1984-89. *Tubercle Lung Dis* 1995;76:205-9.
- 31 Christensen EE, Dietz GW, Ahn CH, et al. Initial roentgenographic manifestations of pulmonary *Mycobacterium tuberculosis*, *M kansasii* and *M intracellulare*. *Chest* 1981;80:132-6.
- 32 Evans AJ, Crisp AJ, Colville A, et al. Pulmonary infections caused by *Mycobacterium mageritense* and *Mycobacterium tuberculosis*: comparison of radiographic features. *AJR* 1993;161:733-7.
- 33 Evans AJ, Crisp AJ, Hubbard RB, et al. Pulmonary *Mycobacterium kansasii* infection: comparison of radiological appearances with pulmonary tuberculosis. *Thorax* 1996;51:1243-7.
- 34 Banks J. Treatment of pulmonary disease caused by non-tuberculous mycobacteria. MD Thesis, University of Manchester, 1988.



- 35 Prussic FHB, Mason AM. Cervical lymphadenitis in children caused by chromogenic mycobacteria. *Can Med Soc J* 1956;75:798-83.
- 36 MacKellar A. Diagnosis and management of atypical mycobacterial lymphadenitis in children. *J Pediatr Surg* 1976;11:85-9.
- 37 Greenberg AE, Kupka E. Swimming pool injuries, mycobacteria and tuberculosis-like disease. *Publ Health Reports* 1957;72:902.
- 38 Meyers WM, Shelly WM, Connor DH, et al. Human *Mycobacterium ulcerans* infections developing at sites of traumatised skin. *J Trop Med Hyg* 1974;23:91.
- 39 Heifets LB. Susceptibility testing of *Mycobacterium avium* isolates. *Antimicrob Agents Chemother* 1996;40:1759-67.
- 40 Heifets LB. Synergistic effect of rifampin, streptomycin, ethionamide and ethambutol on *Mycobacterium intracellulare*. *Am Rev Respir Dis* 1982;125:43-8.
- 41 Banks J, Jenkins PA. Combined versus single antituberculosis drugs on the in vitro sensitivity patterns of non-tuberculous mycobacteria. *Thorax* 1987;42:838-42.
- 42 Banks J, Hunter A, Campbell IA, Smith AP. Pulmonary infection with *Mycobacterium kansasii* in Wales, 1970-9: review of treatment and response. *Thorax* 1983;38:271-4.
- 43 Ahn CH, Lowell JR, Ahn SS, et al. Short course chemotherapy for pulmonary disease caused by *Mycobacterium kansasii*. *Am Rev Respir Dis* 1983;128:1048-50.
- 44 Sauret J, Hernandez-Flix S, Castro E, et al. Treatment of pulmonary disease caused by *Mycobacterium kansasii*: results of 18 vs 12 months' chemotherapy. *Tubercle Lung Dis* 1995;76:104-8.
- 45 Evans SA, Colville A, Evans HA, et al. Pulmonary *Mycobacterium kansasii* infection: comparison of the clinical features, treatment and outcome of pulmonary tuberculosis. *Thorax* 1996;51:1248-52.
- 46 Pang SC. *Mycobacterium kansasii* infections in Western Australia (1982-1987). *Respir Med* 1991;85:213-8.
- 47 White MP, Bangash H, Goel KM, et al. Non-tuberculous mycobacterial lymphadenitis. *Arch Dis Child* 1986;61:368-71.
- 48 Yeager H, Raleigh JW. Pulmonary disease due to *Mycobacterium intracellulare*. *Am Rev Respir Dis* 1973;108:547-52.
- 49 Etzkorn ET, Aldarondo S, McAllister CK, et al. Medical therapy of *Mycobacterium avium-intracellulare* pulmonary disease. *Am Rev Respir Dis* 1986;134:442-5.
- 50 Hunter AM, Campbell IA, Jenkins PA, et al. Treatment of pulmonary infections caused by the *Mycobacterium avium-intracellulare* complex. *Thorax* 1981;36:326-9.
- 51 British Thoracic Society. Treatment of pulmonary infection by *M avium-intracellulare*, *M malmoense* or *M xenopi* with rifampicin plus ethambutol or rifampicin plus ethambutol plus isoniazid: a prospective, multicentre trial. (In preparation for submission).
- 52 Corpe RF. Surgical management of pulmonary disease due to *Mycobacterium avium-intracellulare*. *Rev Infect Dis* 1981;3:1064-7.
- 53 Morna JF, Alexander AG, Staub EW, et al. Long-term results of pulmonary resection for atypical mycobacterial disease and thoracic surgery. *J Thorac Surg* 1983;35:597-604.
- 54 Schaad UB, Votteler TO, McCracken GH, et al. Management of atypical mycobacterial lymphadenitis in childhood: a review based on 380 cases. *J Paediatr* 1979;95:356-60.
- 55 Wolinsky E. Mycobacterial lymphadenitis in children: a prospective study of 105 non-tuberculous cases with long-term follow-up. *Clin Infect Dis* 1995;20:954-63.
- 56 Banks J, Jenkins PA, Smith AP. Infection with *Mycobacterium malmoense*: a review of treatment and response. *Tubercle* 1985;66:197-203.
- 57 France AJ, McLeod DT, Calder MA, et al. *Mycobacterium malmoense* infections in Scotland: an increasing problem. *Thorax* 1987;42:593-5.
- 58 Henriques B, Hoffner SE, Petrini B, et al. Infection of *Mycobacterium malmoense* in Sweden: Report of 221 cases. *Clin Infect Dis* 1994;18:596-600.
- 59 Banks J, Hunter AM, Campbell IA, et al. Pulmonary infection with *Mycobacterium xenopi*. Review of treatment and response. *Thorax* 1984;39:376-82.
- 60 Smith MJ, Citron KM. Clinical review of pulmonary disease caused by *Mycobacterium xenopi*. *Thorax* 1983;38:373-7.
- 61 Griffith DE, Gerard WM, Wallace RJ. Clinical features of pulmonary disease caused by rapidly growing mycobacteria. *Am Rev Respir Dis* 1993;147:1271-8.
- 62 Brown BA, Wallace RJ Jr, Onyi GO, et al. Activities of four macrolides including clarithromycin against *Mycobacterium fortuitum*, *Mycobacterium chelonae*, and *M chelonae-like* organisms. *Antimicrob Agents Chemother* 1992;36:180-4.
- 63 Wallace RJ Jr, Bedsole G, Sumpster G, et al. Activities of ciprofloxacin and ofloxacin against rapidly growing mycobacteria with demonstration of acquired resistance following single drug therapy. *Antimicrob Agents Chemother* 1990;34:65-70.
- 64 Wallace RJ Jr, Swenson JM, Silcox VA, et al. Spectrum of disease due to rapidly growing mycobacteria. *Rev Infect Dis* 1983;5:657-79.
- 65 Rose HD, Dorff GJ, Louwesser M, et al. Pulmonary and disseminated *Mycobacterium smitiae* infection in humans. *Am Rev Respir Dis* 1982;126:1110-3.
- 66 Swenson JM, Wallace RJ Jr, Silcox VA, et al. Antimicrobial susceptibility of five subgroups of *Mycobacterium fortuitum* and *Mycobacterium chelonae*. *Antimicrob Agents Chemother* 1985;28:807-11.
- 67 Wallace RJ Jr, Brown BA, Onyi GO. Susceptibilities of *Mycobacterium fortuitum* biovar. *fortuitum* and the two subgroups of *Mycobacterium chelonae* to imipenem, cefmetazole, cefoxitin and amoxicillin-clavulanic acid. *Antimicrob Agents Chemother* 1991;35:773-5.
- 68 Yew WW, Kwan SYL, Wong PC, et al. Ofloxacin and imipenem in the treatment of *Mycobacterium fortuitum* and *Mycobacterium chelonae* lung infections. *Tubercle* 1990;71:131-3.
- 69 Burns DN, Rohagi PK, Rosenthal R, et al. Disseminated *Mycobacterium fortuitum* successfully treated with combination therapy including ciprofloxacin. *Am Rev Respir Dis* 1990;142:468-70.
- 70 Pacht ER. *Mycobacterium fortuitum* lung abscess: resolution with prolonged trimethoprim/sulphamethoxazole therapy. *Am Rev Respir Dis* 1990;141:s1599-601.
- 71 Ichihama S, Tsukamura M. Ofloxacin and the treatment of pulmonary disease due to *Mycobacterium fortuitum*. *Chest* 1987;92:1110-2.
- 72 Schaefer WB, Wolinsky E, Jenkins PA, et al. *Mycobacterium szulgai*, a new pathogen. *Am Rev Respir Dis* 1973;108:1320-6.
- 73 Wallace RJ, Musser JM, Howell SI, et al. Diversity and sources of rapidly growing mycobacteria associated with infections following cardiac surgery. *J Infect Dis* 1989;159:708-16.
- 74 Hanson P, Thomas J, Collins J. *Mycobacterium chelonae* and abscess formation in soft tissues. *Tubercle* 1987;68:297-9.
- 75 Rappaport W, Dunnington G, Norton L, et al. The surgical management of atypical mycobacterial soft tissue infections. *Surgery* 1990;108:36-9.
- 76 Wallace RJ Jr, Tanner D, Grenin PJ, et al. Clinical trials of clarithromycin for cutaneous (disseminated) infection due to *Mycobacterium chelonae*. *Ann Intern Med* 1993;119:482-6.
- 77 Black MM, Eykyn SJ. The successful treatment of tropical fish tank granuloma (*Mycobacterium marinum*) with cotrimoxazole. *Br J Dermatol* 1977;97:689-92.
- 78 Izumi AK, Hanke CW, Higaki M. *Mycobacterium marinum* infections treated with tetracycline. *Arch Dermatol* 1977;113:1067-8.
- 79 Ramakrishnan L. *Mycobacterium marinum* infection of the hand. *N Engl J Med* 1997;337:612.
- 80 Glynn PJ. The use of surgery and local temperature elevation in *Mycobacterium ulcerans* infection. *Aust NZ J Surg* 1972;41:312-7.
- 81 Portales F, Traore H, Der Ridder K, et al. In vitro susceptibility of *Mycobacterium ulcerans* to clarithromycin. *Antimicrob Agents Chemother* 1998;42:2070-3.
- 82 Modilevsky T, Sattler FR, Barnes PF. Mycobacterial disease in patients with human immunodeficiency virus infection. *Arch Intern Med* 1989;149:2001-5.
- 83 Wallace RJ Jr, O'Brien R, Glassroth J, et al. Diagnosis and treatment of disease caused by non-tuberculous mycobacteria. *Am Rev Respir Dis* 1990;142:940-53.
- 84 Barbaro DJ, Orcutt VL, Coldiron BM. *Mycobacterium avium-intracellulare* infection limited to the skin and lymph nodes in patients with AIDS. *Rev Infect Dis* 1989;11:1145-8.
- 85 Nightingale SD, Byrd LT, Southern PM, et al. Incidence of *Mycobacterium avium-intracellulare* complex bacteraemia in human immunodeficiency virus positive patients. *J Infect Dis* 1972;165:1082-5.
- 86 Horsburgh CR Jr, Wynne B, Bianchini J, et al. Epidemiology of *Mycobacterium avium-intracellulare* complex bacteraemia in patients enrolled in a placebo-controlled study. 8th International Conference on AIDS 1992: B118 (abstract).
- 87 Hoy J, Mich A, Sanderland M, et al. Quadruple drug therapy for *Mycobacterium avium-intracellulare* bacteraemia in AIDS patients. *J Infect Dis* 1990;161:801-5.
- 88 Levine B, Chaisson RE. *Mycobacterium kansasii*: a cause of treatable pulmonary disease associated with advanced human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1991;114:861-8.
- 89 Pozniak AC, Miller R, Ormerod LP. The treatment of tuberculosis in HIV-infected persons. *AIDS* 1999;13:435-45.
- 90 Horsburgh CR Jr, Selick RM. The epidemiology of disseminated non-tuberculous mycobacterial infection in the acquired immunodeficiency syndrome (AIDS). *Am Rev Respir Dis* 1989;139:4-7.
- 91 Bamberger DM, Driks MR, Gupte MR, et al. *Mycobacterium kansasii* among patients infected with human immunodeficient virus in Kansas City. *Clin Infect Dis* 1994;18:395-400.
- 92 Chaisson RE, Benson CA, Dube MP, et al. Clarithromycin therapy for bacteraemic *Mycobacterium avium* complex disease. A randomised, double-blind, dose-ranging study in patients with AIDS. AIDS Clinical Trials Group Protocol 157 Study Team. *Ann Intern Med* 1994;121:905-11.
- 93 Young LS, Wiviott L, Wu M, et al. Azithromycin for treatment of *Mycobacterium avium* complex infection in patients with AIDS. *Lancet* 1991;338:1107-9.
- 94 Chiu J, Mussbaum J, Bozzette S, et al. Treatment of disseminated *Mycobacterium avium* complex infection in AIDS with amikacin, ethambutol, rifampicin and ciprofloxacin. *Ann Intern Med* 1990;113:358-61.
- 95 Jacobson MA, Yajko D, Northfelt D, et al. Randomised, placebo-controlled trial of rifampicin, ethambutol and ciprofloxacin for AIDS patients with disseminated *Mycobacterium avium* complex infection. *J Infect Dis* 1993;168:112-19; 802 (erratum).
- 96 Kemper CA, Havlir D, Bartock AE, et al. Transient bacteraemia due to *Mycobacterium avium* complex in patients with AIDS. *J Infect Dis* 1994;170:488-93.



- 97 von Reyn CF, Pozniak AL. Infections due to the *Mycobacterium avium* complex (MAC). In: Malin A, McAdam KPW, eds. *Ballier's clinical infectious diseases: mycobacterial diseases. Part I: Clinical frontiers*. Volume 4, No. 1. London: Ballière Tindall, 1997: 25–61.
- 98 Low N, Pozniak AL. Current controversies in the therapy for *Mycobacterium avium* complex disease. *J HIV Combination Ther* 1997;2:7–15.
- 99 Claydon EJ, Cocker RJ, Harris JRW. *Mycobacterium malmoense* infection in HIV positive patients. *J Infect* 1991;23:191–4.
- 100 Fakih M, Chapalmadugu S, Ricard A, et al. *Mycobacterium malmoense* bacteraemia in two AIDS patients. *J Clin Microbiol* 1996;34:731–3.
- 101 Shafer RW, Sierra MF. *Mycobacterium xenopi*, *Mycobacterium fortuitum*, *Mycobacterium kansasii* and other non-tuberculous mycobacteria in an area of endemicity for AIDS. *Clin Infect Dis* 1992;15:161–2.
- 102 Nightingale SD, Cameron DW, Gordin FM, et al. Two controlled trials of rifabutin prophylaxis against *Mycobacterium avium* complex infection in AIDS. *N Engl J Med* 1993;329:828–33.
- 103 Pierce M, Crampton S, Henry D, et al. A randomised trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced acquired immunodeficiency syndrome. *N Engl J Med* 1996;335:384–91.
- 104 Havlir DV, Dube MB, Sattler FR, et al. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin or both. *N Engl J Med* 1996;335:392–8.
- 105 Bishai WR, Graham NMH, Harrington G, et al. Rifampicin-resistant tuberculosis in a patient receiving rifabutin prophylaxis. *N Engl J Med* 1996;334:1573–6.