Mycobacterium avium complex in patients with HIV infection in the era of highly active antiretroviral therapy

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Disseminated Mycobacterium avium complex (MAC) infection is the most common bacterial opportunistic infection in adults infected with HIV-1 in the developed world, with an annual frequency of 10–20% in those who have AIDS.1,2 Disseminated MAC appears late in the course of HIV disease and is an independent predictor of mortality, even after adjustment for CD4 lymphocyte count.3 Before the availability of effective treatment, survival among patients with disseminated MAC was short (median 107–134 days)1,3. The development of specific combination therapies for MAC has improved not only bacteriological responses, but also patient survival.4,5 Additionally, prophylaxis for MAC has been shown to significantly reduce disease frequency and enhance patient survival. In recent years, the annual rate of disseminated MAC, and that of other opportunistic infections, has fallen substantially as a result of the availability of highly active antiretroviral therapy (HAART).6,7 However, individuals with HIV infection and advanced immunosuppression who are not receiving or are unable to tolerate HAART continue to be at risk for disseminated MAC, and clinicians caring for HIV-infected patients should be familiar with the prevention and management of this important complication of AIDS.

Clinical features and the effect of HAART

Soon after inhalation or ingestion of MAC organisms from the environment, the infection spreads via local lymphatics, eventually disseminating haematogenously.8 The bacteria are taken up by mononuclear phagocytic cells throughout the body, and reticuloendothelial organs such as the liver, spleen, and bone marrow are the most frequently affected sites.8 Consequently, the clinical presentation of disseminated MAC commonly includes fever, night sweats, and weight loss, and respiratory and gastrointestinal symptoms, and abnormal laboratory values, including raised serum alkaline phosphatase and lactate dehydrogenase, and reduced haemoglobin levels.9,10

Figure 1. Incidence of MAC infection in patients with a CD4 count <200/μL in the Johns Hopkins HIV clinic cohort, 1991–2003 (methods are described in Moore and Chaisson12).
Although the clinical presentation of disseminated MAC might mimic that of disseminated tuberculosis, several clinical features have been proposed to distinguish between the two disease entities. A prospective cohort study involving 22 cases of disseminated tuberculosis and 15 cases of disseminated MAC reported that clinical features that favoured disseminated tuberculosis included the presence of night sweats, peripheral lymphadenopathy, acid-fast bacilli in sputum smears, chest radiographic findings of hilar enlargement, and an absence of previous AIDS-defining illnesses. Clinical features that favoured the diagnosis of disseminated MAC included hepatosplenomegaly, elevated serum alkaline phosphatase (more than twice the upper limit of normal), elevated gamma-glutamyl transpeptidase (more than three times the upper limit of normal), and leucopenia. However, these findings should be interpreted with caution because of the small number of patients studied, and because Mycobacterium tuberculosis infection is much more prevalent in many developing parts of the world where culture diagnosis is not possible.

In addition to causing significant morbidity in patients with AIDS, infection with MAC results in increased hospital admission, necessitates toxic and expensive treatment, and shortens survival. Analysis of a retrospective cohort of 2081 HIV-infected adults revealed that MAC infection was associated with increased mortality independently of CD4 count (relative hazard [RH] 2·56, 95% confidence intervals [CI] 2·1–3·1), presumably because the disease is a marker of immune system failure and disseminated infection carries additional morbid effects. The advent of HAART has changed the natural history of HIV infection in areas of the world where this treatment is accessible. Mortality rates among HIV-infected patients fell from 29·4 per 100 person-years in 1995 to 8·8 per 100 person-years in 1997, with stepwise reductions in morbidity and mortality associated with increases in the intensity of antiretroviral therapy, particularly with the inclusion of highly potent antiviral agents, such as protease inhibitors. Moreover, the rate of disseminated MAC has fallen significantly, coincident with the widespread use of both HAART and specific chemoprophylaxis.

The rate of MAC infection among HIV-infected patients fell substantially after the introduction of HAART in several cohorts. Figure 1 shows the frequency of disseminated MAC in patients from the 1991–2003 Johns Hopkins HIV cohort whose CD4 cell counts were less than 200 cells/µL. The frequency was 7–9% from 1991 to 1993 and then began to fall. Steep reductions were recorded from 1996 onwards, with a current rate of roughly 0·5 cases per 100 person-years. A multivariate Cox proportional hazards analysis shows that predictors of developing disseminated MAC in this cohort of patients with CD4 cell counts less than 200 cells/µL are enrolment between 1990 and 1995, younger age, and no use of HAART (table 1). Figure 2 shows survival after MAC diagnosis in the Johns Hopkins HIV cohort, which improved from a median of 215 days before 1996 to 319 days after 1996. Although this represents significantly longer survival, the outlook in this cohort is still poor. Thus, the major effect of HAART has been in the primary prevention of disease, rather than in survival after diagnosis. However, for patients who are able to take antiretroviral therapy and who do not have multidrug-resistant HIV, extended survival after MAC can be achieved.

**Prophylaxis**

**Criteria for initiating primary prophylaxis**

Before the development of effective chemoprophylaxis, up to 40% of HIV-infected patients developed disseminated MAC within 2 years of the diagnosis of AIDS. HIV-infected adults who have a CD4 cell count of less than 50 cells/mL are at heightened risk for MAC infection and should receive chemoprophylaxis. Although official guidelines do not include criteria for prophylaxis on the basis of HIV plasma RNA (viral load)
measurements, it seems that patients with high viral loads are at significantly heightened risk for MAC infection.\textsuperscript{19-20} The Adult and Adolescent Spectrum of HIV Disease Project Investigators found that HIV-infected patients with viral loads between 55 000 and 149 999 copies/mL had a relative risk (RR) of 3.2 (95% CI 1.5–7.0), and those with viral loads greater than 150 000 copies/mL had a RR of 3.9 (95% CI 1.8–8.4) for developing non-tuberculous mycobacteriosis, independently of CD4 count.\textsuperscript{21} Moreover, a retrospective analysis of four antiretroviral therapy studies found that baseline viral loads correlated significantly with the risk of opportunistic infections, including MAC, pneumocystis, and cytomegalovirus.\textsuperscript{22} Specifically, patients with baseline viral loads greater than 100 000 copies/mL were found to have a RR of 3.13 for developing MAC infection (CI 1.49–6.57, p=0.003) and early reductions of viral load within 8 weeks after initiation of treatment were associated with a significantly reduced risk of MAC infection (RR=0.23, p=0.004).\textsuperscript{23} Whereas patients with high viral loads might have impaired cellular immune function as a result of unchecked viral replication, those who develop MAC uniformly have very low CD4 cell counts. Therefore, prophylaxis for MAC infection should not be prescribed because of high viral loads in patients who do not otherwise meet CD4 criteria for initiation of chemoprophylaxis, although monitoring of CD4 levels might need to be more frequent in such individuals. Additionally, criteria for discontinuation of prophylaxis based on virological suppression alone have not been defined.

**Regimens**

Rifabutin, a semi-synthetic rifamycin with substantial activity against MAC in vitro and in animal models,\textsuperscript{24,25} was the first drug found to have some benefit in preventing MAC infection in patients with AIDS.\textsuperscript{26} Two multicentre, randomised, double-blind, placebo-controlled trials showed that rifabutin (300 mg daily) prophylaxis significantly reduced the rate of MAC bacteremia from 17–18% to 8–9% in patients with AIDS.\textsuperscript{27} Additionally, rifabutin prophylaxis was associated with a significant delay in the development of laboratory abnormalities, including a fall in haemoglobin level and raised alkaline phosphatase, and clinical symptoms, including fatigue, fever, poor performance score, and hospital admission. In these studies, there was no significant difference in adverse events between the two groups. During the roughly 200-day mean follow-up for these two cohorts, the mortality rates were not found to be significantly different, but the number of deaths was low.\textsuperscript{28} However, a subsequent study that extended the follow-up found that rifabutin prophylaxis was associated with a 26% reduction in the risk of death.\textsuperscript{29}

Although rifabutin represented a significant advance in prophylaxis for MAC infection, its slight efficacy, and other disadvantages, including numerous potential drug interactions, high cost, absence of widespread availability, requirement for daily treatment, and potential for the development of rifampicin cross-resistance in tuberculosis patients\textsuperscript{30} stimulated investigation into alternative prophylaxis regimens.

<table>
<thead>
<tr>
<th>Table 2. Indications for starting and stopping prophylaxis and treatment for MAC infection in HIV-infected patients</th>
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<tr>
<td><strong>Indication</strong></td>
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<td>Prophylaxis</td>
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<td>Treatment of disseminated infection</td>
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The macrolide antibiotics azithromycin and clarithromycin have become the mainstay of prophylaxis for HIV-infected patients. Moreover, azithromycin prophylaxis reduces the risk of *Pneumocystis carinii* pneumonia\textsuperscript{31} and bacterial infections,\textsuperscript{32,33} and clarithromycin prophylaxis reduces the risk of bacterial respiratory tract and soft tissue infections by 44%, and also significantly reduces mortality.\textsuperscript{34}

Azithromycin is an azalide antibiotic that achieves low serum levels but is concentrated in macrophages, the primary cells infected by MAC; the drug has a long half-life in tissue, permitting once per week dosing.\textsuperscript{27} Two multicentre, randomised, double-blind studies have investigated the efficacy of once per week azithromycin (1200 mg) in the prevention of MAC infection in patients with AIDS and CD4 cell count less than 100 cells/µL.\textsuperscript{27,28} Oldfield and co-workers\textsuperscript{27} found a significantly higher number of cases of MAC infection in the placebo group than in the azithromycin group (24.7% vs 10.6%, respectively; hazard ratio [HR] =0.34; p=0.004). Although mortality and time to death did not differ, patients in the azithromycin group were significantly less likely to die from MAC infection than placebo recipients (10.5% vs 31.6%; p=0.025). The most common adverse effects associated with azithromycin use were gastrointestinal (79% of azithromycin recipients, 28% of placebo recipients).\textsuperscript{27} A trial by Havlir and co-workers\textsuperscript{35} compared the efficacy of once per week azithromycin (1200 mg) with daily rifabutin (300 mg) or both drugs as chemoprophylaxis against MAC infection. At 1-year follow-up, azithromycin reduced the risk of MAC disease by almost 50% compared with rifabutin (15.3% with rifabutin and 7.6% with azithromycin). The combination of both drugs was even more effective in preventing MAC infection than rifabutin alone (HR 0.28; p=0.001) or azithromycin alone (HR 0.53; p=0.03); however, dose-limiting toxic effects were significantly more common with the two-drug combination than with azithromycin alone (HR 1.67; p=0.03). Among the patients in whom azithromycin prophylaxis was unsuccessful, 11% of MAC isolates were resistant to azithromycin. Overall survival was closely similar in all three groups.\textsuperscript{36}

Clarithromycin, another macrolide antibiotic, has likewise been found to be very effective for the prevention of MAC infection in patients with AIDS.\textsuperscript{37,38} A randomised, placebo-controlled, double-blind study found that prophylaxis with clarithromycin (500 mg twice daily) reduced the rate of MAC bacteremia by 69% (6% in the clarithromycin group vs 16% in the placebo group; adjusted
administration of these two agents could be challenging.33 Interaction between clarithromycin and rifabutin, safe co-
of uveitis, notably at the higher dose of rifabutin was generally well tolerated, combination treatment was
chemoprophylaxis with either clarithromycin or rifabutin failed, 29% and 27% of MAC isolates, respectively, were
resistant to clarithromycin, suggesting that the addition of rifabutin to clarithromycin did not significantly reduce the
development of clarithromycin resistance. Although chemoprophylaxis with either clarithromycin or rifabutin was generally well tolerated, combination treatment was associated with reduced tolerance and heightened frequency of uveitis, notably at the higher dose of rifabutin (450 mg daily). Because of the two-way pharmacokinetic interaction between clarithromycin and rifabutin, safe co-
administration of these two agents could be challenging.33

Based on these studies, current guidelines recommend clarithromycin 500 mg twice daily or azithromycin 1200 mg per week as first-line agents for the prevention of disseminated MAC in HIV-infected patients with a CD4 cell count less than 50 cells/μL (table 3).34 An alternative regimen is rifabutin 300 mg daily or azithromycin 1200 mg per week plus rifabutin 300 mg daily. Alternative doses of clarithromycin and azithromycin are possible, although they have not been studied in human trials for MAC prophylaxis. An extended release clarithromycin is available and has been approved by the Food and Drug Administration in a dose of 1 g daily for the treatment of respiratory tract infections.34,35 On the basis of pharmacokinetics and in vitro susceptibility data, this dose should be effective for preventing MAC. Azithromycin administered as a 600 mg daily dose has been shown to have moderate activity in treating disseminated MAC (see below), and would probably be effective for prophylaxis, although cost and tolerance could be problematic. There are no data supporting the activity or effectiveness of lower daily doses of either clarithromycin or azithromycin. Regrettably, no studies comparing azithromycin with clarithromycin have been undertaken, nor are any likely. Thus, the choice of agent is based on perceptions of relative convenience, cost, tolerability, and effectiveness.

Discontinuation of primary prophylaxis

Because of concerns about potential incomplete restoration of immunological function in patients whose CD4 cell count rose significantly in response to antiretroviral therapy,36 earlier guidelines recommended indefinite continuation of primary prophylaxis for MAC infection.32 Subsequent studies have investigated the safety of discontinuing primary chemoprophylaxis against MAC in patients whose CD4 cell counts, in response to HAART, have risen above threshold values for the initiation of prophylaxis.37

A multicentre, double-blind, randomised, placebo-controlled trial investigated the role of continued chemoprophylaxis with azithromycin (1200 mg per week) in HIV-infected patients who had a median nadir CD4 cell count of 23 cells/μL, which rose to greater than 100 cells/μL in response to antiretroviral therapy.38 During a median follow-up of 12 months, there were no cases of confirmed MAC disease in either the azithromycin–treated group or in the placebo group, and neither the rate of progression of HIV disease nor the mortality rate differed significantly between the two groups (2-0 deaths per 100 person-years in each group). However, the frequency of adverse effects was significantly higher in the group receiving azithromycin than in the group receiving placebo (7-4% vs 1-1%, respectively; p=0-002).38

Another randomised, double-blind, placebo-controlled trial of discontinued versus sustained prophylaxis with azithromycin 1200 mg per week in HIV-infected patients who experienced a sustained rise in CD4 cell count to greater than 100 cells/μL similarly showed no difference in MAC infection rates between the two groups during a 16-month follow-up.39 Additionally, treatment discontinuation because of adverse events was significantly higher in the azithromycin group than in the placebo group (8% vs 2%). Thus, continuation of MAC prophylaxis in the setting of immune reconstitution after initiation of HAART confers no benefit, and increases pill burden, costs, and the potential for drug toxicity and selection of drug-resistant organisms. Based on the findings of these studies, the current recommendations are that primary prophylaxis for MAC can be withdrawn safely in HIV-infected patients whose CD4 cell counts have risen to greater than 100/μL for more than 3 months in response to antiretroviral therapy.38 Primary prophylaxis should be reintroduced if the CD4 cell count falls to less than 50–100 cells/μL.40 The prospect of stopping prophylactic drugs can serve as a powerful incentive for promoting adherence to antiretroviral drugs in patients with advanced HIV disease.

Table 3. Regimens for the prevention of MAC infection in patients with advanced HIV infection

<table>
<thead>
<tr>
<th>Preferred regimens</th>
<th>Alternative regimens</th>
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<tr>
<td>Clarithromycin 500 mg twice daily (or 1000 mg extended release once daily)</td>
<td>Rifabutin 300 mg once daily</td>
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<tr>
<td>Azithromycin 1200 mg once per week</td>
<td>Azithromycin 500–600 mg once daily</td>
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which is now regarded as the cornerstone of any potent regimen.40–44 ACTG 157 was a randomised, double-blind, dose-ranging study in HIV-infected patients with MAC bacteremia who were assigned to three different dosage regimens of clarithromycin (500, 1000, and 2000 mg twice daily) for 12 weeks.44 Time to clearance of bacteremia was faster at higher doses but was equivalent in all three groups after 6 weeks of treatment; paradoxically, however, survival was greater in patients assigned to the lowest dose of clarithromycin (500 mg twice daily). Median survival at this dosage was 249 days compared with 215 days for the 1000 mg dose and 203 days for the 2000 mg dose.45 In another clinical trial, patients with disseminated MAC were randomly assigned to receive clarithromycin at either 500 mg or 1000 mg twice daily plus ethambutol, and either rifabutin or clofazimine.46 The study arm with patients assigned to clarithromycin 1000 mg twice daily was discontinued early because of excess mortality, with 43% of patients dying compared with 22% of patients receiving clarithromycin 500 mg twice daily. The mechanism of increased mortality with higher doses of clarithromycin, despite potent antitubercular activity, is not known, and no specific organ system-related toxicity was suggested in these trials. Nevertheless, in view of the risks associated with higher doses and the equivalent clinical and bacteriological efficacy of lower doses,47 the maximum dose of clarithromycin for treatment of MAC bacteremia in patients with AIDS should be 500 mg twice daily.

Combination treatment for disseminated MAC is mandatory because clarithromycin monotherapy carries an unacceptably high rate of relapse with clarithromycin-resistant strains.48,49 In the ACTG 057 study, clarithromycin-resistant MAC isolates were detected in 46% of patients at a median of 16 weeks.46 In another series of patients with AIDS and disseminated MAC infection receiving clarithromycin alone, 25% of patients who had experienced initial clearance of bacteremia eventually relapsed microbiologically, and more than 50% of these patients were found to have clarithromycin-resistant isolates.46 Therefore, the focus of later investigations was to identify additional companion drugs to be used in combination with clarithromycin to prevent the emergence of macrolide resistance.

Rifabutin also seems to be effective in the treatment of disseminated MAC.60–64 In a 14-day trial of early bacteriological activity in patients with AIDS and MAC bacteremia, 70% of patients receiving rifabutin achieved at least a 0.5 log reduction in MAC colony forming units in blood versus 8% of placebo patients (p=0·002).64 In a prospective, placebo-controlled study, addition of rifabutin (600 mg daily) to a regimen of ethambutol and clofazimine resulted in microbiological responses in seven of 11 patients versus none of 13 patients receiving ethambutol and clofazimine alone (p=0·001) after 4 weeks of treatment, with much the same findings after 12 weeks of treatment.65 The efficacy of rifabutin in a clarithromycin-based regimen was assessed in a large randomised study comparing a three-drug regimen of rifabutin (600 mg daily), ethambutol (roughly 15 mg/kg daily), and clarithromycin (1000 mg twice daily) with a four-drug regimen containing rifampicin (600 mg daily), ethambutol (about 15 mg/kg daily), clofazimine (100 mg daily), and ciprofloxacin (750 mg twice daily).66 The three-drug clarithromycin-based regimen was found to be better than the four-drug regimen with respect to blood culture-negativity at 4 weeks (78% vs 40% of patients; p<0·001) and survival (median 8-6 months vs 5.2 months; p=0·001). The most noteworthy adverse event was the development of uveitis, which happened exclusively in the three-drug group and was associated with high-dose rifabutin (p<0.001).67 By contrast with the findings of other investigations in which patients received clarithromycin alone,60–62 no patients in the three-drug group developed relapse of MAC bacteremia after 16 weeks of treatment.68 This investigation showed the importance of combination treatment with clarithromycin in the treatment of MAC disease as a means to diminish the frequency of clarithromycin resistance.

By contrast with prophylaxis, clinical trials comparing the efficacy of clarithromycin and azithromycin for the treatment of disseminated MAC infection in HIV-infected patients have been undertaken.69–72 In a randomised, open-label trial of HIV-infected patients with MAC bacteremia comparing daily azithromycin plus ethambutol with daily clarithromycin plus ethambutol, clearance of bacteremia was recorded more than 16 weeks of treatment in 38% of azithromycin-treated patients and in 86% of clarithromycin-treated patients (p=0·007).69 Moreover, the estimated median time to sterilisation of blood cultures was 4.4 weeks for clarithromycin recipients versus >16 weeks for azithromycin recipients (p=0·0018). There was no significant difference between the two treatment groups with respect to clinical symptoms, laboratory abnormalities, or adverse effects.73 Although this study found that clarithromycin was better than azithromycin in producing resolution of MAC bacteremia, a larger, randomised, double-blind study comparing the two drugs found comparable microbiological and clinical responses.73 In this study, HIV-infected patients with MAC bacteremia received either azithromycin (250 or 600 mg daily) or clarithromycin (500 mg twice daily), each combined with ethambutol, for 24 weeks. The azithromycin 250 mg arm of the study was discontinued prematurely after an interim analysis revealed a lower rate of blood sterilisation. After 24 weeks of treatment, blood culture-negativity (defined as two consecutive negative cultures) was achieved in 46% of azithromycin recipients and in 56% of clarithromycin recipients (p=0·24). There was no significant difference between the azithromycin group and the clarithromycin group with respect to disease relapse (39% vs 27%, respectively; p=0·21) or mortality (69% vs 63%, respectively; HR 1·1, 95% CI 0·7–1·7).74 Notably, this study was small and the trends seen tended to favour clarithromycin. The weight of evidence suggests that clarithromycin is a more potent drug than azithromycin for the treatment of MAC bacteremia in AIDS, although azithromycin is clearly effective as well.

Several studies have attempted to investigate the contribution of adding one versus two companion drugs to macrolide-containing regimens with respect to the rate of
relapse, emergence of resistance, and survival.\textsuperscript{15,16} In a prospective, placebo-controlled trial, Gordin and co-workers\textsuperscript{15} studied the relative efficacy of clarithromycin (500 mg twice daily) plus ethambutol (1200 mg daily), with or without rifabutin (300 mg daily) for the treatment of MAC bacteraemia in patients with AIDS. There was no difference between the two groups with respect to microbiological response after 16 weeks of treatment (63\% of patients in the rifabutin group vs 61\% in the placebo group; $p=0.81$), changes in clinical symptoms, or survival. However, among patients who experienced a bacteriological response after 16 weeks, there was a reduction in clarithromycin-resistance in the rifabutin-containing arm (2\% of MAC isolates in the three-drug arm vs 14\% in the clarithromycin-ethambutol arm; $p=0.055$). Therefore, although inclusion of rifabutin in a clarithromycin-containing regimen seems to have no effect on bacteriological response or survival, it might protect against development of clarithromycin-resistance in patients who respond to treatment.\textsuperscript{16}

In a multicentre, randomised, open-label trial (ACTG 223), patients with AIDS and MAC bacteraemia were randomly assigned to receive clarithromycin 500 mg twice daily with either ethambutol 15 mg/kg once daily (C+E) or rifabutin 450 mg once daily (C+R), or both (C+E+R) for 48 weeks.\textsuperscript{17} There was no significant difference among the groups after 12 weeks of treatment with respect to complete microbiological response (defined as two consecutive blood cultures negative for MAC without evidence of relapse: 40\% in the C+E group, 42\% in the C+R group, and 51\% in the C+E+R group; $p=0.454$). However, the frequency of relapse was substantially higher in the C+R group (24\%) than in the C+E+R group (6\%; $p=0.027$) and the C+E group (7\%; $p=0.057$). By contrast with the findings of Gordin and colleagues,\textsuperscript{15} the addition of rifabutin in the three-drug regimen did not appear to delay or prevent the emergence of clarithromycin resistance. Patients receiving the three-drug regimen had improved survival compared with the C+E group (HR 0.44, 95\% CI 0.23–0.83) and the C+R group (HR 0.49, 95\% CI 0.26–0.92).\textsuperscript{17} Discrepancies between the findings of Gordin and colleagues\textsuperscript{15} and ACTG 223\textsuperscript{17} could be attributable to differences in study design and patient population. Whereas Gordin and co-workers defined complete microbiological response as either a single negative blood culture or a 1 log\textsubscript{10} fall in bacteraemia from baseline level,\textsuperscript{15} ACTG 223 used the criterion of two consecutive blood cultures negative for MAC.\textsuperscript{17} Additionally, patients were followed for longer in the ACTG study, which might have helped with the ability to detect survival differences among the treatment arms.\textsuperscript{17} ACTG 223 also used a higher rifabutin dose, which might have reduced clarithromycin concentrations as a result of interaction between the two drugs,\textsuperscript{17} thus increasing the probability of clarithromycin resistance, and potentially enhancing the microbiological and overall activity of the three-drug arm in that study.\textsuperscript{17}

Other drugs, including clofazimine, the aminoglycoside antibiotics, and the fluoroquinolones, have also been assessed for the treatment of disseminated MAC in patients with AIDS. Clofazimine was studied in combination with rifabutin early in the HIV epidemic for the treatment of patients with AIDS and MAC infection.\textsuperscript{18} In a small study of 13 patients given clofazimine 100 mg daily and rifabutin 150 mg or 300 mg daily, bacteraemia persisted for a median of 92 days and blood culture-negativity was ultimately achieved in only six of the 13 patients. Two of these six patients later had microbiological relapses, despite continuing the original treatment regimen, and conversion to culture-negativity was associated with clinical improvement in only one patient.\textsuperscript{18}

The role of clofazimine as a companion drug in clarithromycin-based regimens against disseminated MAC in patients with AIDS was investigated in two studies.\textsuperscript{19,20} In a randomised, open-label clinical trial involving outpatients with AIDS and MAC bacteraemia, patients were given clarithromycin 500 mg twice daily and ethambutol 800–1000 mg daily, and were randomly assigned to receive clofazimine 100 mg daily or no clofazimine.\textsuperscript{20} Although both regimens showed equal efficacy in achieving culture-negativity and improvement in clinical symptoms, there was a significantly higher mortality among patients receiving the three-drug regimen than those receiving the two-drug regimen (61\% of three-drug patients died vs 38\% of two-drug patients, $p=0.032$). Although patients randomly assigned to the three-drug regimen had significantly higher baseline MAC colony counts in blood than patients receiving two drugs, a multivariate analysis revealed that assignment to clofazimine, and high baseline MAC colony counts, were independently associated with death ($p<0.05$).\textsuperscript{20} In another study, patients with AIDS and MAC bacteraemia were randomly assigned to receive clarithromycin 2 g/day and ethambutol 20 mg/kg daily, with or without clofazimine 200 mg/day.\textsuperscript{21} There were no significant differences in microbiological responses, or in patient survival between the two treatment groups, but the study was discontinued prematurely because of the findings of the preceding study indicating greater mortality with clofazimine,\textsuperscript{21} and the detection of differences was restricted by the small number of patients enrolled. Because clofazimine does not seem to provide any microbiological benefit and might increase mortality, current recommendations discourage the use of clofazimine for the treatment of MAC disease.\textsuperscript{21}

The aminoglycoside antibiotics have been studied alone and as companion drugs in non-macrolide-based therapies, for example in combination with rifampicin, in patients with HIV infection, and other drug regimens have been suggested for macrolide-resistant infections. The table outlines the preferred and additional drugs used in treatment of HIV patients with disseminated MAC infection.

### Table 4. Regimens for the treatment of disseminated MAC disease in patients with HIV infection

<table>
<thead>
<tr>
<th>Preferred regimens</th>
<th>Additional drugs for macrolide-resistant infections</th>
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<tbody>
<tr>
<td>Clarithromycin 500 mg twice daily or 1000 mg extended release once daily &amp; ethambutol 15 mg/kg daily (or rifabutin 300 mg once daily)</td>
<td>Moxifloxacin 400 mg daily, or Levofloxacin 500–750 mg once daily &amp; $\geq$ 15 mg/kg daily</td>
</tr>
<tr>
<td>Azithromycin 600 mg once daily &amp; ethambutol 15 mg/kg daily (or rifabutin 300 mg once daily)</td>
<td>&amp; intravenous amikacin 10–15 mg/kg daily</td>
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combination regimens for the treatment of MAC bacteraemia in patients with AIDS.†2–30 Nightingale and colleagues7 investigated the efficacy of three different doses of liposome-encapsulated gentamicin (1·7, 3·4, and 5·1 mg/kg) given intravenously twice per week for 4 weeks to patients with AIDS and MAC bacteraemia. All three treatment groups experienced reductions in MAC colony counts in blood by 75% (p<0·005) and no drug-resistant isolates were detected during the study period. Transient renal insufficiency in one patient was the only adverse event noted.31 In another small, prospective, non-randomised study of 17 patients with AIDS and MAC infection, patients received amikacin (7·5 mg/kg intravenously daily) for the first 4 weeks, in combination with ciprofloxacin (750 mg twice daily), ethambutol (1000 mg daily), and rifampicin (600 mg daily) for at least 12 weeks.32 With the use of this combination treatment, baseline geometric mean colony counts from blood cultures fell from 537/mL to 14/mL after 4 weeks of treatment (p<0·001). Microbiological suppression was sustained during treatment, and was associated with reduced MAC-related systemic symptoms. However, seven of 17 patients withdrew from treatment, most commonly as a result of gastrointestinal intolerance and hepatic toxicity.32 In a randomised, open-label clinical trial of HIV-infected patients with MAC bacteraemia, patients received rifampicin (10 mg/kg daily), ciprofloxacin (500 mg twice daily), clofazamine (100 mg daily), and ethambutol (15 mg/kg daily) for 24 weeks, with or without amikacin (10 mg/kg intravenously or intramuscularly 5 days per week) for the first 4 weeks.33 No difference was detected between the two treatment groups with respect to complete or partial clinical responses at 4 weeks (25% in both treatment groups), culture-negativity at 4 weeks (16%) or at 12 weeks (38%), or median survival (30 weeks in both groups; p=0·83, log-rank).33 In addition to demonstrating the absence of benefit of adding amikacin to a four-drug oral regimen containing rifampicin, ciprofloxacin, clofazamine, and ethambutol, this study highlights the poor microbiological and clinical outcomes in response to combination regimens that do not contain a macrolide.

The fluoroquinolone antibiotics also have been shown to have some efficacy in treating HIV-infected patients with MAC bacteraemia.34–36 However, in these studies the activity of fluoroquinolones against MAC was not assessed independently, but rather as part of a combination regimen including rifabutin and ethambutol, with or without clofazamine. The only clinical trial that directly compared the efficacy of a clarithromycin-based regimen with a four-drug combination regimen including ciprofloxacin was that by Shafran and co-workers (cited above),36 which showed the superiority of the clarithromycin-based regimen with respect to microbiological cure and patient survival. Although clinical data are scarce, there is some evidence that moxifloxacin might have some activity against clarithromycin-resistant strains in mouse models of MAC infection.37

Based on the available clinical data, preferred regimens for the treatment of disseminated MAC in patients with AIDS include the following: (i) clarithromycin 500 mg twice daily plus ethambutol 15 mg/kg daily with or without rifabutin 450 mg once daily; and (ii) azithromycin 500–600 mg daily plus ethambutol 15 mg/kg daily (table 4). Regimens involving high-dose clarithromycin (>500 mg twice daily) and clofazamine should be avoided because of the increased mortality associated with these regimens.48,52,53 Although intermittent dosing of clarithromycin-containing regimens has been used successfully to treat other non-tuberculous mycobacterial infections,49 alternative dosing schedules have not been studied specifically for the treatment of MAC bacteraemia in patients with AIDS. Despite the absence of clinical data, some experts recommend that severe cases of MAC bacteraemia be treated with an additional drug, such as ciprofloxacin 500–750 mg twice daily, levofloxacin 500–750 mg once daily, moxifloxacin 400 mg once daily, rifabutin 300 mg daily, or intravenous amikacin 10–15 mg/kg daily. Additionally, anecdotal evidence supports the use of linezolid and melfoxine in refractory cases of disseminated MAC infection.49 Although data on the discontinuation of chronic maintenance treatment for MAC infection are scarce,49,50 these data and clinical evidence from other opportunistic infections49,50 suggest that it is safe to discontinue treatment for MAC infection after completion of a greater than 12-month course, assuming there are no MAC-specific signs and symptoms, and there is a sustained rise (>6 months) in CD4 cell count to greater than 100 cells/μL after HAART.49

A vexing difficulty for clinicians is the treatment of patients with clarithromycin-resistant MAC disease. No formal studies have been undertaken on this condition, and treatment guidelines are non-existent. Some experts recommend continuing clarithromycin based on unpublished evidence that polyclonal infection with both clarithromycin-susceptible and clarithromycin-resistant organisms occurs. Studies in animal models suggest that the combination of fluoroquinolones and ethambutol has synergistic activity against MAC and might, therefore, be useful.42 Suggested treatment for patients with clarithromycin-resistant MAC infection therefore includes a fluoroquinolone (moxifloxacin or levofloxacin) plus ethambutol plus rifabutin. Amikacin could be given initially, although extended treatment is challenging because of toxicity and the need for parenteral administration.

**Future directions**

Significant progress has been made in the last decade in the treatment of HIV and in the prevention and treatment of various opportunistic infections, including MAC. These advances have resulted in a diminished rate of MAC infection in developed countries. However, MAC continues to occur frequently in areas of the world where HAART is unavailable, or in patients who do not have access to or who cannot tolerate HAART, or who have developed drug-resistant HIV infection. For these patients, MAC prophylaxis remains a paramount priority.

Several important questions remain about the prevention and treatment of disseminated MAC in patients with AIDS. For example, unrecognised but potentially significant immunological factors other than CD4 count.
might place patients at heightened risk for disseminated MAC. Although clinical data suggest that very high viral loads are independently associated with heightened risk for disseminated MAC, the usefulness of specific threshold HIV RNA values for initiation of primary prophylaxis has not been studied. Despite the significant success of clarithromycin-based combination regimens in treating MAC bacteraemia, treatment remains complex and extended. Simplification of treatment with dosing—eg, three times per week, merits further investigation, and new drugs with enhanced activity against clarithromycin-resistant strains of MAC are needed. With regard to discontinuation of maintenance treatment, questions remain about the duration of treatment and risk factors for disease recurrence after CD4 counts have risen in response to HAART. In HIV-uninfected patients with pulmonary MAC infection, treatment is recommended for at least 12 months after conversion of cultures. Whether this is appropriate for patients with HIV infection is not clear, although current recommendations use this benchmark. Furthermore, the CD4 threshold for discontinuation of secondary prophylaxis, and the duration of the treatment CD4 count should remain above this threshold before prophylaxis can be safely discontinued need further investigation. Future study in this specialty is complicated by the (fortunately) decreasing frequency of MAC infection in developed countries, but resolution of these outstanding questions will help further reduce the morbidity and mortality associated with disseminated MAC in patients with AIDS.

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Conflicts of interest

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