

Disseminated *Mycobacterium avium* Complex Disease

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Epidemiology

Organisms of the *Mycobacterium avium* complex (MAC) are ubiquitous in the environment.¹⁻⁶ In the era prior to the availability of effective antiretroviral therapy (ART), *M. avium* was the etiologic agent in >95% of people living with HIV with advanced immunosuppression who acquired disseminated MAC disease.^{4,7-12} Recent studies conducted using newer bacterial typing technology suggest organisms causing bacteremia in people with HIV include a diversity of species, including the *M. avium* subspecies *hominissuis* and *M. colombiense*.¹³ An estimated 7% to 12% of adults have previously contracted MAC, although rates of disease vary in different geographic locations.^{2,4,8,11,12} Although epidemiologic associations have been identified, no environmental exposure or behavior has been consistently linked to subsequent risk of developing MAC disease.

The mode of MAC transmission is thought to be through inhalation, ingestion, or inoculation of MAC bacteria via the respiratory or gastrointestinal (GI) tract.^{1,14} Household or close contacts of those with MAC disease do not appear to be at increased risk of disease, and person-to-person transmission is unlikely.

MAC disease typically occurs in people with HIV with CD4 T lymphocyte (CD4) cell counts <50 cells/mm³. The incidence of disseminated MAC disease is 20% to 40% in people with HIV with advanced immunosuppression in the absence of effective ART or chemoprophylaxis.^{15,16} The overall incidence of MAC disease among people living with HIV has continued to decline in the modern ART era to current levels of <2 cases of MAC as the first opportunistic infection [OI] per 1,000 person-years for individuals in care.¹⁷⁻²⁰ In addition to CD4 count <50 cells/mm³, factors associated with increased risk for MAC disease identified in recent studies are plasma HIV RNA levels >1,000 copies/mL, ongoing viral replication despite ART, previous or concurrent OIs, and reduced *in vitro* lymphoproliferative immune responses to *M. avium* antigens, possibly reflecting defects in T-cell repertoire.¹⁸⁻²⁰

Clinical Manifestations

In people living with HIV with advanced immunosuppression who are not on ART, MAC disease often is a disseminated, multi-organ infection, although localized disease may also be seen.²¹⁻²⁵ Early symptoms may be minimal and can precede detectable mycobacteremia by several weeks. Symptoms may include fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain.⁸

Laboratory abnormalities particularly associated with disseminated MAC disease include anemia (often out of proportion to that expected for the stage of HIV disease) and elevated liver alkaline phosphatase levels.^{4,5,7-12,15,16,26,27} Hepatomegaly, splenomegaly, or lymphadenopathy (paratracheal, retroperitoneal, para-aortic, or less commonly peripheral) may be identified on physical examination or by radiographic or other imaging studies. Other focal physical findings or laboratory abnormalities may occur with localized disease.

In comparison to people with HIV who are not receiving or not responding to ART, localized manifestations of MAC disease have been reported more often in people with HIV who are receiving and have responded to ART with an increase in CD4 cell counts, suggesting improved immune function. Localized syndromes include cervical, intraabdominal or mediastinal lymphadenitis, pneumonia, pericarditis, osteomyelitis, skin or soft-tissue abscesses, bursitis, genital ulcers, or central nervous system infection. Localized syndromes may also be manifestations of immune reconstitution inflammatory syndrome (IRIS), as discussed below.

IRIS is recognized as a systemic inflammatory syndrome with signs and symptoms that are clinically indistinguishable from active MAC infection, although bacteremia is generally absent. Similar to tuberculosis (TB), MAC-associated IRIS can occur as “unmasking” IRIS in people with HIV with subclinical (undiagnosed) MAC or “paradoxical” IRIS in those with previously established MAC disease.²⁸⁻³² Both variants occur primarily in those with advanced immunosuppression who begin ART and have a rapid and marked reduction in plasma HIV RNA.^{32,33} The syndrome may be benign and self-limited or may result in severe, unremitting symptoms that improve with the use of systemic anti-inflammatory therapy or corticosteroids.

Diagnosis

A confirmed diagnosis of disseminated MAC disease is based on compatible clinical signs and symptoms coupled with the isolation of MAC from cultures of blood, lymph node, bone marrow, or other normally sterile tissue or body fluids.^{16,24,25,34,35} Species identification should be performed using molecular techniques, polymerase chain reaction-based assays, whole genome sequencing, high-performance liquid chromatography, or biochemical tests.

Other ancillary studies provide supportive diagnostic information, including acid-fast bacilli smear and culture of stool or tissue biopsy material, radiographic imaging, or other studies aimed at isolating organisms from focal infection sites.

Detection of MAC organisms in the respiratory or GI tract may represent colonization of these sites and may be a harbinger of disseminated MAC infection. However, no data are available regarding efficacy of treatment with clarithromycin, azithromycin, rifabutin, or other drugs alone or in combination for asymptomatic colonization with MAC organisms at these sites. Therefore, routine screening of respiratory or GI specimens and pre-emptive treatment for MAC **is not recommended**.

Preventing Exposure

MAC organisms commonly contaminate environmental sources of infection, such as food and water. Available information does not support specific recommendations regarding avoidance of exposure.

Preventing Disease

Indication for Primary Prophylaxis

Primary prophylaxis against disseminated MAC disease **is not recommended** for adults and adolescents with HIV who immediately initiate ART (**AII**). People with HIV who are not receiving ART or who remain viremic on ART but have no current options for a fully suppressive ART regimen should receive chemoprophylaxis against disseminated MAC disease if they have CD4 counts <50 cells/mm³ (**AI**).

Primary MAC prophylaxis, if previously initiated, should be discontinued in adults and adolescents who are continuing on a fully suppressive ART regimen (**AI**). Two randomized, placebo-controlled trials and observational data have demonstrated that people with HIV taking ART can discontinue primary prophylaxis with minimal risk of developing MAC disease.³⁶⁻⁴⁰

This updated recommendation is based on data from recent observational cohort studies. In an analysis of 369 people with HIV with CD4 counts <50 cells/mm³ while on ART and followed for at least six months, the overall incidence of MAC disease was 0.6 per 100 person-months. No MAC occurred among 71 persons on ART who were virologically suppressed at baseline, including 41 persons who were not receiving primary MAC prophylaxis.⁴¹ Another study enrolled 157 people with HIV who had at least one CD4 count <50 cells/mm³ and had started ART between 1998 and 2014. The study compared the incidence of disseminated MAC disease within the 12 months after the first CD4 count <50 cells/mm³ between a group of 33 participants who received primary MAC prophylaxis and a group of 122 participants who received no MAC prophylaxis.²⁰ There were no differences between the groups in the proportion of participants who achieved or the time to achieve a CD4 count >100 cells/mm³ or in the proportion of participants who achieved viral suppression within 12 months. The incidence of MAC disease was not statistically significantly different between the groups; 3.4 per 100 person-years for those on primary prophylaxis versus 0.8 per 100 person-years for those not on primary prophylaxis. In each of these studies, plasma HIV RNA level >1,000 copies/mL was the principal risk factor for developing MAC disease regardless of MAC prophylaxis. In a study from the OI Working Group of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE), the incidence of primary MAC disease was 0.74 per 1,000 person-years (IQ range 0.68 to 0.80) among people living with HIV on ART and not receiving MAC prophylaxis.⁴² These data suggest that primary MAC prophylaxis provides no additional benefit in patients started on effective ART that results in viral suppression. Additional arguments against primary MAC prophylaxis include the potential for increased cost, adverse effects of the drugs used for prophylaxis, and, for the small number of people with HIV who might develop “unmasking MAC IRIS” after starting ART, the use of monotherapy for MAC prophylaxis may result in acquired drug resistance in those with active MAC disease.^{43,44}

Preferred and Alternative Drugs for Prophylaxis

As previously stated, primary prophylaxis for MAC is not recommended, but for those for whom prophylaxis is being considered, azithromycin⁴⁵ and clarithromycin^{5,46} are the preferred prophylactic agents (**AI**).^{1,47} The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and **should not be used (AI)**.⁵ The combination of azithromycin and rifabutin is more effective than azithromycin alone in preventing MAC disease.⁴⁵ However, based on the additional cost, increased occurrence of adverse effects, potential for drug interactions, and no greater survival benefit than with azithromycin alone, the combination regimen of azithromycin and rifabutin **is not recommended (AI)**. Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. In people with HIV who cannot tolerate azithromycin or clarithromycin, rifabutin is an alternative prophylactic agent for MAC disease (**BI**), although drug interactions may complicate use of this agent. Before prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment and if appropriate based on that assessment, by obtaining a blood culture for MAC. TB also should be excluded before rifabutin is used for MAC prophylaxis because treatment with rifabutin monotherapy could result in acquired resistance to *M. tuberculosis* in people with HIV who have active TB.

Treating Disease

Initial treatment of MAC disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance (**AI**).^{1,6,11,12,14,48-56} Clarithromycin is the preferred first agent (**AI**); it has been studied more extensively than azithromycin in people with AIDS and appears to be associated with more rapid clearance of MAC from the blood.^{6,48,50,54,55,57} However, azithromycin can be substituted for clarithromycin when drug interactions or intolerance preclude the use of clarithromycin (**AII**). Testing MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for all people with HIV.^{58,59}

Ethambutol is the recommended second drug for the initial treatment of MAC disease (**AI**). Some clinicians would add rifabutin as a third drug (**CI**). One randomized clinical trial demonstrated that adding rifabutin to the combination of clarithromycin and ethambutol improved survival, and in two randomized clinical trials, this approach reduced emergence of drug resistance^{6,50} in individuals with AIDS and disseminated MAC disease. These studies were completed before the availability of effective ART. Whether similar results would be observed for people with HIV receiving effective ART has not been established. Some experts would recommend the addition of a third or fourth drug in settings in which the risk of mortality is increased and emergence of drug resistance is most likely, such as with advanced immunosuppression (CD4 count <50 cells/mm³), high mycobacterial loads (>2 log₁₀ colony-forming units/mL of blood), and/or the absence of effective ART (**CII**). The third or fourth drug might include a fluoroquinolone such as levofloxacin or moxifloxacin (**CIII**), which have *in vitro* and animal model activity against MAC, or an injectable agent such as amikacin or streptomycin (**CIII**), although no randomized clinical trials have evaluated the added efficacy of these antibiotics in the setting of clarithromycin or azithromycin treatment or effective ART.^{58,60}

Special Considerations with Regard to Starting Antiretroviral Therapy

ART should be started as soon as possible after the diagnosis of MAC disease, preferably at the same time as initiation of antimycobacterial therapy in people with HIV and disseminated MAC disease who are not receiving effective ART (**CIII**). The rationale for starting ART as soon as possible is to reduce the risk of further AIDS-defining OIs and to further improve the response to antimycobacterial therapy in the setting of advanced immunosuppression (**CIII**). If ART has already been initiated, it should be continued. The regimens should be modified when there is any potential for an adverse drug-drug interaction(s) between the antiretroviral and antimycobacterial drugs (**CIII**). People with HIV will need continuous antimycobacterial treatment unless ART results in immune reconstitution.

Monitoring of Response to Therapy and Adverse Events (including IRIS)

A repeat blood culture for MAC should be obtained 4 weeks to 8 weeks after initiating antimycobacterial therapy only in people with HIV who do not have a clinical response to their initial treatment regimens. Improvement in fever and a decline in quantity of mycobacteria in blood or tissue can be expected within 2 weeks to 4 weeks after initiation of appropriate therapy; clinical response may be delayed, however, in those with more extensive MAC disease or advanced immunosuppression.

Adverse effects with clarithromycin and azithromycin include gastrointestinal upset, metallic taste, elevations in liver transaminase levels or hypersensitivity reactions. These adverse effects may be exacerbated when drug levels are increased due to drug interactions associated with rifabutin or some

antiretroviral drugs. Doses of clarithromycin >1 g/day for treatment of disseminated MAC disease have been associated with increased mortality and **should not be used (AI)**.⁶¹ When used with clarithromycin or other drugs that inhibit cytochrome P450 (CYP450) isoenzyme 3A, rifabutin has been associated with a higher risk of adverse drug interactions.^{62,63}

Given complex drug interactions, if rifabutin is used, dose adjustment is necessary in people with HIV receiving protease inhibitors (PIs), efavirenz, rilpivirine, or doravirine; rifabutin should not be used with elvitegravir/cobicistat or bictegravir.⁶⁴⁻⁷¹ No dose adjustment for rifabutin or integrase inhibitors, other than elvitegravir/cobicistat or bictegravir, is currently recommended.^{72,73} The most updated drug-drug interaction information can be found in the [Adult and Adolescent Antiretroviral Guidelines](#). PIs can increase clarithromycin levels, but no recommendation to adjust the dose of either clarithromycin or PIs can be made based on existing data. The ability of efavirenz to induce metabolism of clarithromycin can result in reduced serum concentration of clarithromycin but increased concentration of the 14-OH active metabolite of clarithromycin. Although the clinical significance of this interaction is unknown, it could reduce the efficacy of clarithromycin for MAC prophylaxis. Azithromycin metabolism is not affected by the CYP450 system; azithromycin can be used safely in the presence of PIs, NNRTIs, or integrase inhibitors without concerns about drug interactions.

People with HIV on ART who develop moderate-to-severe symptoms typical of IRIS should receive initial treatment with non-steroidal, anti-inflammatory drugs (**CIII**). If IRIS symptoms do not improve, short-term (4 weeks–8 weeks) systemic corticosteroid therapy, in doses equivalent to 20 to 40 mg of oral prednisone daily, has been successful in reducing symptoms and morbidity (**CII**).^{29,74}

Managing Treatment Failure

MAC treatment failure is defined by the absence of a clinical response and the persistence of mycobacteremia after 4 to 8 weeks of treatment. Repeat testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for people with HIV whose disease relapses after an initial response to treatment. Most people with HIV who experience failure of clarithromycin or azithromycin primary prophylaxis in clinical trials had isolates susceptible to these drugs when MAC disease was detected.^{6,11,12,48,75,76}

Because the number of drugs with demonstrated clinical activity against MAC is limited, results of susceptibility testing should be used to construct a new multidrug regimen. The regimen should consist of at least two new drugs (i.e., not previously used) to which the isolate is susceptible. Drugs from which to choose are rifabutin, an injectable aminoglycoside (amikacin or streptomycin), or a fluoroquinolone (levofloxacin or moxifloxacin), although data supporting a survival or microbiologic benefit when these agents are added have not been compelling (**CII**).^{11,12,49-53,57,77-81} Data in people without HIV who are being treated for MAC indicate that an injectable aminoglycoside (amikacin or streptomycin) is a viable choice (**CIII**).⁵⁸ Continuing clarithromycin or azithromycin despite resistance is generally not recommended as there is likely to be no additional benefit and may be added toxicity. Clofazimine **should not be used** because randomized trials have demonstrated lack of efficacy and an association with increased mortality (**AI**).^{49,51,79} Anecdotal evidence exists for the addition of one or more other second-line agents (e.g., ethionamide, thioacetazone [not available in the United States], cycloserine, or linezolid) to the combination of clarithromycin or azithromycin and other drugs as salvage therapy, but their role in this setting is not well defined. Optimization of ART is an important adjunct to second-line or salvage therapy for MAC disease in people with HIV

for whom initial treatment is unsuccessful or who have disease that is resistant to antimycobacterial drugs (**AIII**).

Adjunctive treatment of MAC disease with immunomodulators has not been thoroughly studied, and data are insufficient to support a recommendation for its routine use.

Preventing Recurrence

People with HIV and disseminated MAC disease should continue chronic maintenance therapy (**AII**) unless ART results in immune reconstitution.^{37,38}

When to Stop Secondary Prophylaxis or Chronic Maintenance Therapy

The risk of MAC recurrence is low in people with HIV who have completed at least a 12-month MAC treatment course, remain asymptomatic with respect to MAC signs and symptoms, and sustain an increase in CD4 count to >100 cells/mm³ for ≥ 6 months after initiation of ART. In this setting, it is reasonable to discontinue maintenance therapy based on data from studies in people with HIV and inferences from more extensive study data that indicate the safety of discontinuing secondary prophylaxis for other OIs (**AI**).^{38,53,82-86} Reintroducing chronic maintenance therapy or secondary prophylaxis for people with HIV for whom a fully suppressive ART regimen is not possible and who have a decline in their CD4 count to levels consistently below 100 cells/mm³ may be indicated (**BIII**).

Special Considerations During Pregnancy

Primary prophylaxis for MAC disease in pregnant women and adolescents is **not recommended** (**AIII**). Because clarithromycin is associated with an increased risk of birth defects based on evidence from certain animal studies, it **is not recommended** as the first-line agent for prophylaxis or treatment of MAC in pregnancy (**BIII**). Two studies, each with slightly more than 100 women with first-trimester exposure to clarithromycin, did not demonstrate an increase in or specific pattern of defects, although an increased risk of spontaneous abortion was noted in one study.^{87,88} Azithromycin did not produce defects in animal studies, but experience is limited with use in humans during the first trimester. A nested case-control study conducted within the large Quebec Pregnancy cohort found an association between azithromycin use and spontaneous miscarriage.⁸⁹ However, the authors were not able to adjust for severity of infection, an important confounder. Multiple studies, including large cohort studies, have found no association between the use of azithromycins in the first trimester and major congenital malformations, include heart defects.⁹⁰⁻⁹² When primary prophylaxis is required for a pregnant woman who is not being treated with effective ART, azithromycin is the preferred agent (**BIII**). For secondary prophylaxis (chronic maintenance therapy), azithromycin plus ethambutol is the preferred drug combination (**BIII**).

Diagnostic considerations and indications for treatment of MAC disease for pregnant women are the same as for women who are not pregnant. On the basis of animal data discussed previously, azithromycin is preferred over clarithromycin as the first-line agent to use in combination with ethambutol for treatment of MAC disease (**BIII**). Use of ethambutol rather than rifabutin or other agents with the potential for drug-drug interactions should allow initiation of ART as soon as possible during pregnancy to decrease the risk of perinatal transmission of HIV. Pregnant women whose MAC disease fails to respond to a primary regimen should be managed in consultation with infectious disease and obstetrical specialists.

Recommendations for Preventing and Treating Disseminated *Mycobacterium avium* Complex Disease

Preventing First Episode of Disseminated MAC Disease (Primary Prophylaxis)

- Primary prophylaxis is **not recommended** for adults and adolescents who immediately initiate ART **(AII)**.

Indications for Initiating Primary Prophylaxis

- Not on fully suppressive ART, *and*
- CD4 count <50 cells/mm³ after ruling out disseminated MAC disease based on clinical assessment (which may include mycobacterial blood culture for some people with HIV) **(AI)**

Preferred Therapy

- Azithromycin 1200 mg PO once weekly **(AI)**, *or*
- Clarithromycin 500 mg PO BID **(AI)**, *or*
- Azithromycin 600 mg PO twice weekly **(BIII)**

Alternative Therapy

- Rifabutin 300 mg PO daily **(BI)** (dose adjustment may be necessary based on drug-drug interactions, please refer to [Table 4](#) for dosing recommendation when used with ARV drugs).
- **Note:** Active TB should be ruled out before starting rifabutin.

Indication for Discontinuing Primary Prophylaxis

- Initiation of effective ART **(AI)**

Indication for Restarting Primary Prophylaxis

- CD4 count <50 cells/mm³ (only if not on fully suppressive ART) **(AIII)**

Treating Disseminated MAC Disease

Preferred Therapy

- At least 2 drugs as initial therapy to prevent or delay emergence of resistance **(AI)**
 - Clarithromycin 500 mg PO twice daily **(AI)** plus ethambutol 15 mg/kg PO daily **(AI)**, *or*
 - Azithromycin 500–600 mg **(AII)** plus ethambutol 15 mg/kg PO daily **(AI)** when drug interactions or intolerance precludes the use of clarithromycin
 - **Note:** Testing of susceptibility to clarithromycin or azithromycin is recommended.

Alternative Therapy

- Some experts would recommend addition of a third or fourth drug for people with HIV with high mycobacterial loads (i.e., >2 log CFU/mL of blood), or in the absence of effective ART **(CIII)**.

The Third or Fourth Drug Options May Include:

- Rifabutin 300 mg PO daily **(CI)** (dose adjustment may be necessary based on drug-drug interactions), *or*
- A fluoroquinolone **(CIII)** (e.g., levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily), *or*
- An injectable aminoglycoside **(CIII)** (e.g., amikacin 10–15 mg/kg IV daily or streptomycin 1 gm IV or IM daily)

Chronic Maintenance Therapy (Secondary Prophylaxis)

- Same as treatment regimens

Criteria for Discontinuing Chronic Maintenance Therapy **(AII)**

- Completed **at least** 12 months therapy, *and*
- No signs and symptoms of MAC disease, *and*
- Have sustained (>6 months) CD4 count >100 cells/mm³ in response to ART

Indication for Restarting Secondary Prophylaxis

- CD4 <100 cells/mm³ **(AIII)**

Other Considerations

- NSAIDs may be used for people with HIV who experience moderate to severe symptoms attributed to IRIS **(CIII)**.
- If IRIS symptoms persist, a short-term course (4 weeks–8 weeks) of systemic corticosteroid (equivalent to prednisone 20–40 mg) can be used **(CII)**.

Key: ART = antiretroviral therapy; ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte; CFU = colony-forming units; IM = intramuscular; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; MAC = *Mycobacterium avium* complex; NSAIDs = non-steroidal anti-inflammatory drugs; PO = orally; TB = tuberculosis

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