

# Disseminated *Mycobacterium avium* Complex Disease

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## Epidemiology

Organisms of the *Mycobacterium avium* complex (MAC) are ubiquitous in the environment.<sup>1-6</sup> In the era before effective antiretroviral therapy (ART) was available, *M. avium* was the etiologic agent in >95% of people with HIV with advanced immunosuppression who acquired disseminated MAC disease.<sup>4,7-12</sup> Newer bacterial typing technology suggests organisms causing bacteremia in people with HIV represent a diversity of species, including the *M. avium* subspecies *hominissuis* and *M. colombiense* and other non-MAC species, including *M. genavense*, *M. kansasii*, *M. simiae*, *M. mycogenicum*, and others.<sup>13-16</sup> These comprise what was historically referred to as disseminated MAC. An estimated 7% to 12% of adults with HIV have been previously infected with MAC, although rates of disease vary in different geographic locations.<sup>2,4,8,11,12</sup> In particular, disseminated MAC in people with HIV has been described more frequently in the United States and Europe than in resource-limited settings.<sup>17</sup>

Although epidemiologic associations with infection have been identified, no singular environmental exposure or behavior has been consistently linked to subsequent increased risk of developing MAC disease. The mode of MAC infection is thought to be through repeated inhalation or ingestion of MAC bacteria via the respiratory or gastrointestinal (GI) tract, likely from environmental exposure.<sup>1,18</sup> 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.<sup>19</sup>

MAC disease typically occurs in people with HIV with CD4 T lymphocyte (CD4) cell counts <50 cells/mm<sup>3</sup>. The previously reported incidence of disseminated MAC disease ranged from 20% to 40% in people with HIV with advanced immunosuppression in the absence of effective ART or chemoprophylaxis.<sup>20,21</sup> However, the overall incidence of MAC disease among people with HIV has declined substantially 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, even among those not receiving effective ART.<sup>22-26</sup> In addition to a CD4 count <50 cells/mm<sup>3</sup>, factors associated with increased risk for MAC disease are ongoing HIV viral replication despite ART, previous or concurrent OIs, reduced *in vitro* lymphoproliferative immune responses to *M. avium* antigens (possibly reflecting defects in T-cell repertoire), and genetic predisposition in some populations.<sup>24-27</sup> While effective ART has clearly been associated with dramatic reductions in risk of developing MAC disease, MAC disease still can occur in people with HIV on suppressive ART, and the clinical presentation may differ from what is seen in people with untreated HIV. In one retrospective case series following people with HIV mostly on ART, nontuberculous mycobacterial (NTM) disease occurred in nine people who were virologically suppressed on ART at the time of their diagnosis—seven with pulmonary NTM only and two with extrapulmonary disease. MAC was the most common NTM pathogen, isolated in 19 of the 34 cases.<sup>13</sup> Those with extrapulmonary disease were younger and had higher viral loads and lower CD4 counts at diagnosis.

## Clinical Manifestations

In people with HIV with advanced immunosuppression who are not on ART, MAC disease generally presents as a disseminated, multi-organ infection, although localized disease may also be seen.<sup>28-32</sup> Early symptoms may be minimal and can precede mycobacteremia or positive tissue cultures by several weeks. Symptoms are nonspecific and include fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain.<sup>8,13-15</sup>

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.<sup>4,5,7-12,20,21,33,34</sup> 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.

Localized MAC disease occurs more often in people with HIV on suppressive ART with increased CD4 counts than in people with HIV not on ART, suggesting improved immune function is associated with more localized disease. Localized syndromes include cervical, intraabdominal, or mediastinal lymphadenitis; pneumonia; pericarditis; osteomyelitis; skin or soft-tissue abscesses; bursitis; genital ulcers; and central nervous system infection. Localized syndromes may also be manifestations of immune reconstitution inflammatory syndrome (IRIS), as discussed below.

## 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 fluid, bone marrow, or other normally sterile tissue or body fluids, although data suggest that bone marrow cultures have low yield for detection of MAC in this setting, particularly if blood cultures are negative.<sup>21,31,32,35-40</sup> 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 tissue, radiographic imaging, or other studies aimed at isolating organisms from focal infection sites.

Although isolated pulmonary MAC disease is not often observed in people with advanced HIV-associated immunosuppression, occasionally MAC disease may be limited to the lung in people with HIV who are virologically suppressed on ART. Diagnostic criteria for disease limited to the lung in this setting should follow those established by the [American Thoracic Society \(ATS\)](#), [European Respiratory Society \(ERS\)](#), [European Society of Clinical Microbiology and Infectious Diseases \(ESCMID\)](#), and the [Infectious Disease Society of America \(IDSA\) joint guideline on Treatment of Nontuberculous Mycobacterial Pulmonary Disease](#), which include pulmonary clinical signs and symptoms, exclusion of other alternative diagnoses, nodular or cavitary disease on lung imaging, and a positive culture for MAC from at least two sputum specimens or at least one bronchoalveolar lavage or biopsy sample.<sup>41</sup>

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 for asymptomatic colonization with MAC organisms at these sites. Therefore, routine screening of respiratory or GI specimens and preemptive 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

### Recommendations for Preventing Disseminated *Mycobacterium avium* Complex Disease

Preventing First Episode of Disseminated MAC Disease (Primary Prophylaxis)
<ul style="list-style-type: none"> <li>Primary prophylaxis is <b>not recommended</b> for adults and adolescents who immediately initiate ART <b>(AII)</b>.</li> </ul> <p><b>Indications for Primary Prophylaxis</b></p> <ul style="list-style-type: none"> <li>CD4 count &lt;50 cells/mm<sup>3</sup> <b>AND</b> not receiving ART or remains viremic on ART or has no options for a fully suppressive ART regimen <b>(AI)</b></li> <li>Before primary prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment, and if appropriate, by obtaining a blood culture for MAC <b>(AI)</b>. If blood culture is obtained, prophylaxis should be delayed until results are available to avoid exposing patients to monotherapy and the attendant risk of drug resistance <b>(AI)</b>.</li> </ul> <p><b>Preferred Therapy</b></p> <ul style="list-style-type: none"> <li>Azithromycin 1,200 mg PO once weekly <b>(AI)</b>, <i>or</i></li> <li>Clarithromycin 500 mg PO twice daily <b>(AI)</b>, <i>or</i></li> <li>Azithromycin 600 mg PO twice weekly <b>(BIII)</b></li> </ul> <p><b>Alternative Therapy</b></p> <ul style="list-style-type: none"> <li>Rifabutin 300 mg PO daily <b>(BI)</b> in people who cannot tolerate azithromycin or clarithromycin <ul style="list-style-type: none"> <li>Dose adjustment of rifabutin may be necessary based on drug–drug interactions, please refer to <a href="#">Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines</a> for dosing recommendation when used with certain ARV drugs.</li> <li>Active TB should be ruled out before starting rifabutin to avoid monotherapy in the setting of active TB.</li> </ul> </li> </ul> <p><b>Indication for Discontinuing Primary Prophylaxis</b></p> <ul style="list-style-type: none"> <li>If previously initiated, primary prophylaxis should be discontinued if the patient is continuing on a fully suppressive ART regimen <b>(AI)</b>.</li> </ul>
Pregnancy Considerations
<ul style="list-style-type: none"> <li>During pregnancy, if ART is immediately initiated, then primary prophylaxis for MAC disease is <b>not recommended (AIII)</b>.</li> <li>When primary prophylaxis is required because of the absence of effective ART, azithromycin is the preferred agent <b>(BIII)</b>.</li> </ul>

**Key:** ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; MAC = *Mycobacterium avium* complex; PO = orally; TB = tuberculosis

## ***Indication for Primary Prophylaxis***

Primary prophylaxis against disseminated MAC disease **is not recommended** for adults and adolescents with HIV who immediately initiate ART, regardless of CD4 count (**AI**). People with HIV who have CD4 counts  $<50$  cells/mm<sup>3</sup> and who are not receiving ART, remain viremic on ART, or have no options for a fully suppressive ART regimen should receive chemoprophylaxis against disseminated MAC (**AI**). 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. MAC prophylaxis should be delayed until results are available to avoid exposing patients to monotherapy and the attendant risk of drug resistance (**AI**).

## ***When to Stop Primary Prophylaxis***

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 several large observational cohort studies have demonstrated that people with HIV taking ART can discontinue primary prophylaxis with minimal risk of developing MAC disease, particularly if they are virologically suppressed.<sup>42-47</sup> Conclusions from these studies indicate that the overall incidence of disseminated MAC within 6 to 12 months after stopping primary prophylaxis in these circumstances, regardless of CD4 count, was 0.6 to 0.8 per 100 person-years. 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. However, in a study from the TREAT Asia HIV Observational Database, which evaluated the impact of MAC prophylaxis on AIDS-defining conditions and HIV-associated mortality in people with HIV on ART from September 2015 onward, macrolide use within 3 months of starting ART for those with a CD4 count  $<50$  at ART initiation was associated with a decreased risk of HIV-associated mortality (HR 0.10; 95% CI, 0.01–0.80; P = 0.031) but not with the combined outcome of developing an AIDS-defining condition or death.<sup>48</sup> Despite this finding, only 10.6% of the 1,345 participants in the cohort eligible for MAC prophylaxis received it. The authors concluded that there may be an additive protective effect of macrolide prophylaxis in reducing overall HIV-related mortality among Asians with HIV and CD4 counts  $<50$  even though they received effective ART. Despite some differences among these published data, for most individuals, particularly in higher resourced settings, the preponderance of current data suggest that primary MAC prophylaxis provides no additional benefit in people started on effective ART that results in viral suppression. Additional arguments against primary MAC prophylaxis while prioritizing effective ART to achieve viral suppression include (1) the potential for adding additional cost and adverse effects of the drugs used for prophylaxis; (2) the likelihood that only a small number of people with HIV will develop “unmasking MAC IRIS” (i.e., active MAC disease after starting ART); (3) the potential for acquired drug resistance if people fail monotherapy for MAC prophylaxis; and (4) limiting polypharmacy to assist with adherence to ART.<sup>49-51</sup>

## ***Preferred and Alternative Drugs for Prophylaxis***

As previously stated, primary prophylaxis for MAC is not recommended for people on effective ART, but for those for whom prophylaxis is being considered, azithromycin<sup>52</sup> and clarithromycin<sup>5,53</sup> are the preferred prophylactic agents (**AI**).<sup>1,54</sup> 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**).<sup>5</sup> The combination of azithromycin and rifabutin is more effective than azithromycin alone in preventing MAC disease.<sup>52</sup> However, based on the additional cost, increased occurrence of adverse effects, potential for drug

interactions, and lack of greater survival benefit than with azithromycin alone, the combination regimen of azithromycin and rifabutin is **not recommended (AI)**. In people with HIV who cannot tolerate azithromycin or clarithromycin, rifabutin can be used as a prophylactic agent for MAC disease (**BI**), although drug interactions may complicate use of this agent. Moreover, tuberculosis (TB) should be excluded before rifabutin is used to avoid monotherapy in the setting of active TB, which could result in acquired rifamycin resistance.

## Treating Disease

### Recommendations for Treating Disseminated *Mycobacterium avium* Complex Disease

Treating Disseminated MAC Disease
<p><b>Preferred Therapy</b></p> <ul style="list-style-type: none"> <li>• At least two drugs as initial therapy to prevent or delay emergence of resistance (<b>AI</b>) <ul style="list-style-type: none"> <li>○ Clarithromycin 500 mg PO twice daily (<b>AI</b>) plus ethambutol 15 mg/kg PO daily (<b>AI</b>), <i>or</i></li> <li>○ Azithromycin 500–600 mg (<b>AII</b>) plus ethambutol 15 mg/kg PO daily (<b>AI</b>) when drug interactions or intolerance precludes the use of clarithromycin (<b>AII</b>)</li> <li>○ <b>Note:</b> Testing of susceptibility to clarithromycin or azithromycin is recommended.</li> </ul> </li> <li>• Some experts would add rifabutin when more severe disease manifestations are present. <ul style="list-style-type: none"> <li>○ Rifabutin 300 mg PO daily (<b>CI</b>). Dose adjustment of rifabutin may be necessary based on drug–drug interactions. Refer to the <a href="#">Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB</a> table in the <i>Mycobacterium tuberculosis</i> section for more information.</li> </ul> </li> <li>• Some experts would also add a fourth drug if more severe disease is present, the risk of mortality is high, emergence of drug resistance is likely (e.g., after failure of MAC prophylaxis), CD4 count is &lt;50 cells/mm<sup>3</sup>, mycobacterial loads are high (&gt;2 log<sub>10</sub> CFU/mL of blood), or effective ART is absent (<b>CIII</b>). Fourth drug options may include: <ul style="list-style-type: none"> <li>○ A fluoroquinolone (<b>CIII</b>) (e.g., levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily), <i>or</i></li> <li>○ An injectable aminoglycoside (<b>CIII</b>) (e.g., amikacin 10–15 mg/kg IV daily or streptomycin 1 g IV or IM daily) (generally avoided unless in the setting of refractory disease when other alternatives are not available or tolerated)</li> <li>○ Bedaquiline, tedizolid, linezolid, and omadacycline have demonstrated <i>in vitro</i> activity against clinical isolates of MAC; these might also be considered in people with refractory MAC disease.</li> </ul> </li> </ul> <p><b>Duration of Therapy</b></p> <ul style="list-style-type: none"> <li>• At least 12 months (<b>AII</b>)</li> <li>• Shorter duration may be considered depending on the degree of immunologic recovery following initiation of ART. CD4 count should be &gt;100 cells/mm<sup>3</sup> for ≥6 months before discontinuation of therapy (<b>CIII</b>).</li> </ul> <p><b>Chronic Maintenance Therapy (Secondary Prophylaxis)</b></p> <ul style="list-style-type: none"> <li>• Same as treatment regimens</li> <li>• If ART does not result in immune reconstitution, people with HIV and disseminated MAC disease should continue chronic maintenance therapy (<b>AII</b>).</li> </ul> <p><i>Criteria for Discontinuing Chronic Maintenance Therapy (Secondary Prophylaxis) (AI)</i></p> <ul style="list-style-type: none"> <li>• Completed <b>at least</b> 12 months of therapy, <i>and</i></li> </ul>

- No signs or symptoms of MAC disease, *and*

- Have sustained ( $\geq 6$  months) CD4 count  $>100$  cells/mm<sup>3</sup> in response to ART

*Indication for Restarting Chronic Maintenance Therapy (Secondary Prophylaxis)*

- If a fully suppressive ART regimen is not possible and CD4 is consistently  $<100$  cells/mm<sup>3</sup> (**BIII**)

#### Pregnancy Considerations

- For secondary prophylaxis (chronic maintenance therapy), azithromycin plus ethambutol is the preferred drug combination (**BIII**).

#### Other Considerations

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

**Key:** ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CFU = colony-forming units; IM = intramuscular; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; MAC = *Mycobacterium avium* complex; NSAID = nonsteroidal anti-inflammatory drug; PO = orally

Initial treatment of MAC disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance (**AI**).<sup>1,6,11,12,18,55–63</sup> Clarithromycin (**AI**) or azithromycin (**AII**) are preferred first agents; published data are more extensive for clarithromycin than for azithromycin in people with advanced HIV disease, and clarithromycin appears to be associated with more rapid clearance of MAC from the blood.<sup>6,55,57,61,62,64</sup> However, azithromycin is acceptable when drug interactions or intolerance preclude the use of clarithromycin (**AII**). Doses of clarithromycin  $>1$  g/day for treatment of disseminated MAC disease have been associated with increased mortality and **should not be used (AI)**.<sup>65</sup> Testing MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for all people with HIV, particularly those who developed MAC disease while receiving prophylaxis with one of these agents.<sup>66,67</sup> In three randomized clinical trials, clarithromycin-resistant isolates were reported in 29% and 58% of people with HIV who developed MAC bacteremia during prophylaxis with clarithromycin, and azithromycin-resistant isolates were recovered from 11% of those who developed bacteremia while on azithromycin prophylaxis.<sup>5,52,53,68</sup> More advanced immunosuppression at prophylaxis initiation and longer duration of MAC prophylaxis are associated with higher rates of clarithromycin resistance at the time of MAC prophylaxis failure.<sup>68</sup>

Ethambutol is the recommended second drug for the initial treatment of MAC disease (**AI**) based on randomized trials of MAC therapy that indicate its use in the regimen is associated with lower rates of relapse.<sup>56,58,64,69</sup> Rifabutin can be used as a third drug (**CI**) with or without a fluoroquinolone (levofloxacin or moxifloxacin) (**CIII**), or an injectable aminoglycoside (amikacin or streptomycin) (**CIII**) can be used as a fourth drug if more severe disease is present; the risk of mortality is high; emergence of drug resistance is likely (e.g., after failure of MAC prophylaxis); or in the setting of advanced immunosuppression (CD4 count  $<50$  cells/mm<sup>3</sup>), high mycobacterial loads ( $>2$  log<sub>10</sub> colony-forming units/mL of blood), or the absence of effective ART (**CIII**). 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<sup>6,57</sup> in individuals with advanced HIV and disseminated MAC disease. These studies were completed before the availability of effective ART. It has not been established whether similar results would be observed for people with HIV receiving effective ART. The fluoroquinolones levofloxacin and moxifloxacin and amikacin have *in vitro* and animal model

activity against MAC, although randomized trials evaluating the efficacy of adding a fluoroquinolone or injectable aminoglycoside as part of a multidrug regimen for treatment of MAC have not been done. Injectable aminoglycosides should generally be avoided except in the setting of refractory disease when other alternative agents are not available or tolerated.<sup>66,70</sup> Additional drugs with *in vitro* activity against clinical isolates of MAC include bedaquiline, tedizolid, linezolid, and omadacycline; these might also be considered in people with refractory MAC disease.<sup>71-75</sup>

While not specifically applicable to people with HIV (who more often have disseminated MAC disease than isolated pulmonary disease), in 2020, the ATS/ERS/ESCMID/IDSA updated their jointly sponsored [clinical guideline for treatment of nontuberculous mycobacterial pulmonary disease](#), including pulmonary MAC.<sup>41</sup> People with HIV fully suppressed on ART with higher CD4 counts may present with localized pulmonary or other local organ system MAC disease that may clinically resemble such disease in people without HIV. Following the ATS/ERS/ESCMID/IDSA guidelines would be reasonable in such settings. The recommended treatment includes an initial three-drug regimen containing a macrolide and ethambutol for those with macrolide-susceptible pulmonary MAC disease. Addition of an aminoglycoside, which in refractory cases can be given as inhalation suspension, is recommended if cavitory or severe bronchiectatic disease is present or if macrolide resistance is suspected.<sup>76</sup>

People with HIV and disseminated MAC disease should be treated for a minimum duration of 12 months (**AII**). Shorter duration of treatment may be considered depending on the degree of immunologic recovery following initiation of ART (**CIII**); the CD4 count should be maintained above 100 cells/mm<sup>3</sup> for at least 6 months before discontinuing MAC treatment.<sup>77-79</sup>

### ***Special Considerations Regarding Antiretroviral Therapy Initiation***

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 (**BIII**). ART is recommended as soon as possible to reduce the risk of further AIDS-defining OIs and to further improve the response to antimycobacterial therapy in the setting of advanced immunosuppression (**BIII**). 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 (ARV) and antimycobacterial drugs (**BIII**). Information on [drug–drug interactions](#) can be found in the Adult and Adolescent Antiretroviral Guidelines. People with HIV will need continuous antimycobacterial treatment until ART results in sustained immune reconstitution, as indicated above (CD4 count maintained above 100 cells/mm<sup>3</sup> for at least 6 months).

### ***Monitoring of Response to Therapy and Adverse Events (Including IRIS)***

A repeat blood culture for MAC should be obtained 4 to 8 weeks after initiating antimycobacterial therapy in people with HIV who do not have a clinical response to their initial treatment regimens. Improvement in fever and other systemic symptoms and a decline in quantity of mycobacteria in blood or tissue can be expected within 2 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 of clarithromycin and azithromycin include GI upset, metallic taste, elevations in liver transaminase levels, and hypersensitivity reactions. Clarithromycin's adverse effects may be exacerbated when drug levels are increased due to drug interactions associated with some ARV

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)**.<sup>65</sup> Protease inhibitors (PIs) can increase clarithromycin levels; clarithromycin dose adjustment or switching clarithromycin to azithromycin may be necessary. Azithromycin metabolism is not affected by the cytochrome P450 (CYP) system; azithromycin can be used safely in the presence of PIs, non-nucleoside reverse transcriptase inhibitors, or integrase inhibitors without concerns about drug interactions.

When used with clarithromycin or other drugs that inhibit CYP isoenzyme 3A4, rifabutin has been associated with a higher risk of adverse drug interactions, in particular sight-threatening uveitis and neutropenia.<sup>80-82</sup> Rifabutin adverse effects are concentration related; therapeutic drug level monitoring may be considered to reduce the potential for adverse effects. Rifabutin must be dose adjusted in people with HIV receiving PIs or efavirenz. Rifabutin should not be coadministered with cobicistat-boosted PIs, long-acting injectable cabotegravir/rilpivirine, bicitegravir, elvitegravir/cobicistat, fostemsavir, or lenacapavir.<sup>82-86</sup> Rilpivirine and doravirine must be dose adjusted if either is coadministered with rifabutin. No dose adjustment for rifabutin or the integrase inhibitors dolutegravir or raltegravir or injectable cabotegravir alone is currently recommended, although at least one study suggested that compared with people without TB or MAC, lower trough concentrations were observed when once daily dolutegravir was used together with rifabutin.<sup>87-89</sup> The most updated drug–drug interaction information can be found in the [Adult and Adolescent Antiretroviral Guidelines](#). Therapeutic drug monitoring may be helpful for optimizing drug dosing in the context of complex drug–drug interactions.<sup>90</sup>

IRIS associated with MAC disease is recognized as a systemic inflammatory syndrome, with signs and symptoms clinically indistinguishable from active MAC infection, although bacteremia is generally absent. Similar to 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.<sup>91-95</sup> Both variants occur primarily in those with advanced immunosuppression who begin ART and have a rapid and marked reduction in plasma HIV RNA.<sup>95,96</sup> Elevated alkaline phosphatase levels may be a predictor of MAC-associated IRIS.<sup>97</sup> 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.

People with HIV on ART who develop moderate to severe symptoms typical of IRIS should receive initial treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) (**BIII**). If IRIS symptoms do not improve, short-term (4–8 weeks) systemic corticosteroid therapy, in doses equivalent to 20 to 40 mg of oral prednisone daily, can be used to reduce symptoms and morbidity (**BII**).<sup>92,98</sup> Severe forms of MAC IRIS with a hemophagocytic lymphohistiocytosis (HLH) phenotype may occur, and a lower hemoglobin prior to ART may help predict this more severe form of IRIS.<sup>97,99</sup> Patients with this more severe form may have a genetic predisposition, and cases of MAC IRIS and other NTM IRIS requiring additional immunosuppression in addition to corticosteroids have been reported.<sup>99,100</sup>

### ***Managing Treatment Failure***

MAC treatment failure is defined by the absence of a clinical response and the persistence of mycobacteremia (or persistently positive tissue cultures from other sites) 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.

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 include rifabutin, fluoroquinolone (levofloxacin or moxifloxacin), an injectable aminoglycoside (amikacin or streptomycin), or possibly bedaquiline, tedizolid, linezolid, or omadacycline, although data supporting a survival or microbiologic benefit when these agents are added are limited.<sup>11,12,41,56-60,64,69,72-75,101-104</sup> Continuing clarithromycin or azithromycin despite resistance **is not recommended (BIII)**, as there is likely to be no additional benefit and may have added toxicity. Clofazimine **should generally not be used** because randomized trials have demonstrated lack of efficacy and an association with increased mortality **(AI)**.<sup>56,58,69</sup> 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)**.

Although anecdotal data and individual case reports suggest potential benefit, adjunctive treatment of MAC disease with immunomodulators has not been thoroughly studied, and data are insufficient to support a recommendation for routine use, except in the setting of familial immunodeficiencies associated with increased risk of MAC disease.<sup>105</sup>

## Preventing Recurrence

As indicated above, people with HIV and disseminated MAC disease should be treated for a minimum duration of 12 months **(AII)**. Shorter duration of treatment may be considered depending on the degree of immunologic recovery following initiation of ART; the CD4 count should be maintained above 100 cells/mm<sup>3</sup> for at least 6 months before discontinuing MAC treatment. If ART initiation does not result in immune reconstitution, people with HIV and disseminated MAC disease should continue chronic maintenance therapy **(AII)**.<sup>77-79</sup>

## *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/mm<sup>3</sup> 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)**.<sup>44,60,77-79,106-108</sup> 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/mm<sup>3</sup> may be indicated **(BIII)**.

## Special Considerations During Pregnancy

During pregnancy, if ART is being immediately initiated, then primary prophylaxis for MAC disease **is not recommended (AIII)**. When primary prophylaxis is required because of the absence of effective ART, azithromycin is the preferred agent **(BIII)**. For secondary prophylaxis (chronic maintenance therapy), azithromycin plus ethambutol is the preferred drug combination **(BIII)**. 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.<sup>109,110</sup>

Azithromycin did not produce defects in animal studies, but experience with use in humans during the first trimester is limited. A nested case-control study conducted within the large Quebec Pregnancy cohort found an association between azithromycin use and spontaneous miscarriage<sup>111</sup>; 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 azithromycin in the first trimester and major congenital malformations, including heart defects.<sup>112-114</sup> A systematic review of pregnancy outcomes following macrolide use found no significant increased risks for major congenital malformations or congenital heart defects following all macrolide use in the first trimester, but a small but significant increased rate of major congenital malformations with azithromycin though maternal confounders could not be excluded. In a Cochrane systematic review of *Chlamydia trachomatis* infection treatment in pregnancy, there was no apparent difference between azithromycin and other agents in terms of efficacy and pregnancy complications.<sup>115</sup>

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