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Mycobacterium Avium Complex

Medical Science

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ABSTRACT

Atypical mycobacterial infection has been described in the medical literature since 1950s.The development and introduction of a rapid radiometric mycobacterial detection system has enabled the distinction of mycobacterium tuberculosis from other mycobacteria, allowed antimicrobial susceptibility testing and advanced the field of mycobacteriology. The increased frequency of atypical mycobacterial infection stems from advances in diagnostic procedures1.

INTRODUCTION

Mycobacterium avium complex (MAC) consists of several related species of mycobacterium that are ubiquitous in environment. *Mycobacterium avium* complex (MAC) is an **opportunistic infection** caused by species of *Mycobacterium* that can cause severe illness in people with advanced AIDS but rarely affects others. The risk of disseminated MAC (DMAC) is directly related to the severity of **immunosuppression**. DMAC typically occurs in persons with CD4 counts of <50 cells/μL, and its frequency increases as the CD4 count declines. In the absence of antibiotic prophylaxis, DMAC occurs in up to 40% of AIDS patients with CD4 counts of <50 cells/μL. Antimicrobial therapy, especially if given in conjunction with antiretroviral therapy (ART) that achieves immune reconstitution, can be successful in treating MAC disease.

MICROBIOLOGY

Mycobacterium avium complex (MAC) is a group of genetically related bacteria belonging to the genus Mycobacterium.

It includes

- *Mycobacterium avium*
- *Mycobacterium intracellulare*
- Other species of mycobacterium that have not been classified.

The separation of M.avium from M.intracellulare is diffficult as it relies on **serotyping.** Therefore they are sometimes commonly referred as M. avium intracellulare.

- Sero types(total 28)2

1. M.avium 1,2,3,4,5,6,8,9,10,11,21
2. M.intracellulare 7,12,13,14,15,16,17,18,19,20,25
3. Not classified 22,23,24,26,27,28

- Some sources also include *Mycobacterium avium subspecies paratuberculosis(MAP).*

Mycobacterium avium is the only important subspecies associated with human infection, whereas *M avium paratuberculosis* has been associated with **Crohn's disease**. MAC strains vary in pathogenicity which may explain why M.avium types 4 and 8 are most common organisms to infect the patients with AIDS3. Markers of pathogenicity of the organism include the presence of plasmid antibiotic susceptibility patterns, restriction fragment length polymorphism patterns and multifocus enzyme electrophoretic patterns 4, 5.

EPIDEMIOLOGY

MAC is ubiquitous in distribution. They are found worldwide and have been isolated from soil, water, animals, birds, and foods.6 The common environmental sources of MAC include aerosolized water, piped hot water systems (including household and hospital water supplies), bathroom shower heads, house dust, soil, birds, farm animals, and cigarette components such as tobacco, filters, and paper. **Risk factors** for acquisition of MAC infection include using an indoor swimming pool, consumption of raw or partially cooked fish or shellfish, bronchoscopy and treatment with granulocyte stimulating factor.

It is generally a **saprophytic** organism, entry is usually via the **GI tract** but can also be via the lungs and disseminates to cause multisystem infection. The risk of developing DMAC has been inversely correlated with absolute CD4 lymphocyte count values.

The most important risk factor for MAC infection in patients

without HIV infection is **underlying lung disease** like lung cancer, chronic obstructive pulmonary disease (COPD), chronic bronchitis, bronchiectasis, cystic fibrosis, mitral valve prolapse. Pulmonary disease is the most common manifestation of MAC infection in these patients. MAC has also been associated with the pulmonary infection and bronchiectasis in elderly women (of the middle lobe, lingula, or both) without a pre-existing lung disease, also referred to as **Lady Windermere syndrome**.

Deficiency of IFN-gamma and TNF-alpha production and absence or defects of IFN-gamma receptors are also associated with infections with MAC and other mycobacteria. Familial outbreaks have been reported in association with genetic defects related to IFN-gamma receptors.

Less commonly, MAC has been associated with **hot-tub** lung, a type of hypersensitivity pneumonitis like lung disease due to pulmonary response to infectious aerosols of MAC found in water.

Race: MAC infection has **no racial predilection**.7 Sex: *M intracellulare* is more pathogenic and tends to infect women increasingly beyond menopause. Age: Children are at risk of developing lymphadenitis secondary to MAC infection.

PATHOGENESIS

MAC in patients is theorized to represent **recent acquisition** rather than latent infection reactivating7, 8, 9. MAC can invade and translocate across the mucosal epithelium. The bacteria subsequently infect the resting macrophages in the ***lamina propria*** and spread in the submucosal tissue; they are then carried to the local **lymph nodes** by lymphatics. In immunocompromised hosts, such as patients with AIDS, they are subsequently spread hematogenously to the liver, spleen, bone marrow, and other sites.

MAC dissemination requires a susceptible host. In **non –HIV** infected population MAC infection generally presents as localized infection: **cervical lymphadenitis** in children which is generally unilateral, the node is firm at beginning, but a collarstud abscess is formed eventually which is characteristic blue purple in colour with multiple discharging sinuses. Right middle lobe or lingular **bronchiectasis** in women having narrow anteroposterior chest diameter, pectus excavatum, scoliosis or mitral valve prolapse.10,11 Similar picture in elderly women is believed to be due to voluntary cough suppression that results in stagnation of secretions, which is suitable for growth of the organisms, referred to as Lady Windermere syndrome

Suprisingly histopathologic examination of liver, spleen, bone marrow or intestine from patients with AIDS related DMAC shows high grade infection yet a **lack of inflammatory infiltrate** of tissue necrosis. In contrast, HPE of AIDS patients with localized infection demonstrate marked inflammatory reaction and tissue destruction similar to that of non-HIV associated MAC lung or lymph node infection. The lack of inflammatory response in AIDS patients having DMAC is consistent with the hypothesis that the key immunologic defects associated with dissemination are **defective macrophage killing** of phagocytized MAC and aberrant cytokine responses, including low levels of tumor necrosis factor, gamma interferon and interleukin-12.12,13

CLINICAL PRESENTATION

M avium complex (MAC) infection usually presents **in 1 of 3 forms**: (1) pulmonary MAC infection in immunocompetent hosts, (2) disseminated MAC (DMAC) infection in individuals with advanced AIDS, or (3) MAC lymphadenitis in children.

Pulmonary MAC infection in immunocompetent hosts generally manifests as cough, sputum production, weight loss, fever, lethargy, and night sweats. The onset of symptoms is insidious. Symptoms may be present for weeks to months. Many patients have only a chronic cough with purulent sputum production. **Hemoptysis is rare** in MAC infection.

Patients with advanced AIDS and **DMAC** infection commonly present with fever of unknown origin **(FUO).** They usually also have sweating, weight loss, fatigue, anorexia, diarrhea, shortness of breath, and right upper quadrant abdominal pain. Abdominal pain or chronic diarrhea results from involvement of retroperitoneal lymph nodes or gut mucosa respectively. Hepatosplenomegaly, lymphadenopathy and (rarely) jaundice also may be present.

The chest X ray is abnormal in 25% of patients, most common radio graphic pattern is bilateral lower lobe interstitial infiltrate suggestive of miliary spread. In addition alveolar, nodular infiltrate, hilar or mediastinal adenopathy occurs. **Anemia** which can be severe is the **most common laboratory anomaly** and leukopenia, elevated alkaline phosphatase levels or low albumin occurs in some patients.

Less common manifestations of MAC infection in patients with AIDS have included mastitis, pyomyositis, cutaneous abscess, palatal and gingival ulceration, septic arthritis, osteomyelitis, bursitis, tenosynovitis, endophthalmitis, pericarditis, peritonitis(in patients with cirrhosis), brain abscess, GI mycobacteriosis and massive GI hemorrhage15,16,17,18,19. Immune reconstitution syndrome associated with MAC has been reported in patients with underlying MAC infection presenting shortly after the introduction of HAART.

MAC lymphadenitis is predominantly a disease of children aged 1-4 years, primarily involving unilateral cervical lymph nodes. It usually involves submandibular and submaxillary lymph nodes, although preauricular, postauricular, and submental nodes may also be affected. Rarely, infection of the axillary, epitrochlear, or inguinal lymph nodes may develop following direct cutaneous inoculation. The lymph nodes usually enlarge insidiously but may enlarge more rapidly in younger children. Generally, they resolve spontaneously. The lymph nodes may also caseate and rupture through the skin, forming a sinus tract with chronic discharge.

PHYSICAL FINDINGS

Physical findings in MAC infection depend on the form of infection and the patient. In immunocompetent patients with **pulmonary MAC infection**, generally lung crackles, rhonchi, or both can be heard on auscultation. Additionally, depending on the type of lung lesion and severity of infection, patients with pulmonary MAC infection may have tachypnea, dullness on chest percussion, or bronchial breath sounds.

DMAC infection in patients with AIDS can cause generalized wasting, skin pallor, tender hepatosplenomegaly, and lymphadenopathy.

Lymphadenitis in children can cause unilateral enlargement of submandibular, preauricular, parotid, and/or postauricular lymph nodes. They are usually multiple and rubbery to firm and may appear to be fixed to the deeper structures. They may become matted together as the disease progresses. The overlying skin may appear shiny, thin, and erythematous or violaceous. Sinus tracts may be present in advanced cases. Patients with synovitis may present with pain and swelling of a joint or features of bursitis or tenosynovitis.

DIAGNOSIS

LAB STUDIES

At least 3 **sputum specimens**, preferably early-morning samples taken on different days, should be collected for acid-fast bacil-

lus (AFB) staining and culture. Sputum AFB stains are positive for *M avium* complex (MAC) in most patients with **pulmonary MAC infection**.Bronchoscopy and bronchoalveolar lavage can also be considered. Mycobacterial cultures grow MAC in about 1-2 weeks, depending on the culture technique and bacterial burden.

Diagnosis of **MAC lymphadenitis** is based on a high level of clinical suspicion and **biopsy** of the nodes with histological and microbiological confirmation. Fine-needle aspiration of lymph nodes has been used to obtain tissue for diagnosis when complete excision is not feasible.

Blood cultures in appropriate mycobacterial culture media should be performed for suspected disseminated MAC **(DMAC)** infection20. This should be performed routinely in patients with advanced AIDS and persistent undiagnosed febrile illness. One blood culture identifies 91% of patients with MAC bacteremia, a second blood culture increases the identification rate to 98%. (57) Therefore, obtaining paired or more than 2 sequential blood specimens for culture to diagnose MAC bacteremia is unnecessary. The preferred culture method includes lysis of peripheral blood leukocytes to release intracellular mycobacteria followed by inoculation onto solid media (eg, **Lowenstein-Jensen, Middlebrook 7H11 agar**) or into radiometric broth.Cultures generally take 1-2 weeks to turn positive21,22. In addition, DNA probes can identify MAC species within 2 hours once sufficient mycobacterial growth has occurred in radiometric broth or on solid media2

Biopsies from other normally sterile body sites also can prove diagnostic23. Stains of biopsy specimens from bone marrow, lymph node, or liver may demonstrate acid-fast organisms or granuloma weeks before positive blood culture results are obtained. Results of acid-fast staining of tissue or pus are usually negative because of the small number of bacilli.

Mycobacterial susceptibility testing studies have shown poor correlations between in vitro susceptibility results and clinical outcome, the ATS/IDSA guidelines recommend routine antibiotic susceptibility for clarithromycin only.

Because MAC may take weeks to grow in culture, **ancillary studies** should be performed. These are not specific, but may be helpful in reaching a presumptive diagnosis:Complete blood count (CBC) for anemia, lymphopenia, thrombocytopenia, Serum alkaline phosphatase (often elevated in DMAC). An enzyme immunoassay **(EIA)** kit used in Japan has been used to detect serum IgA antibody to MAC-specific glycopeptidolipid core antigen.Sensitivity and specificity of this EIA kit were reported as 84% and 100%, respectively

IMAGING STUDIES

Patients with pulmonary MAC infection with underlying lung disease often have cavities revealed by imaging studies. Typically, these patients have **fibrocavitary changes** and nodules that involve the upper lung zones. Elderly women without underlying lung disease but with MAC pulmonary infection develop a fibronodular bronchiectasis that often involves the lingula and right middle lobe.

Other radiological changes include atelectasis, consolidation, **tree-in-bud appearance**, and ground-glass opacities. In patients with AIDS and DMAC infection, **CT scan** of the abdomen reveals retroperitoneal or periaortic **lymphadenopathy14** and hepatosplenomegaly.

Hypersensitivity pneumonitis like changes characterized by **ground-glass attenuation**, centrilobular nodules, and air trapping on expiratory images are seen on CT scans in patients with hot-tub lung, which is a type of hypersensitivity pneumonitis like reaction.

Histologic Findings

Histologic findings of MAC infection include necrotizing and nonnecrotizing **granulomas** and positive AFB smear results. Numbers of AFB are usually higher in MAC infection than in *M tuberculosis* infection

ATS/IDSA guidelines for the diagnosis of non tuberculous mycobacterial pulmonary infection

Clinical guidelines:

Pulmonary signs and symptoms such as cough, fatigue, weight loss; less commonly, fever and weight loss and dyspnea are present. Exclusion of other diseases (eg, carcinoma, tuberculosis) is essential.

Radiographic guidelines:

Chest radiograph with nodular or cavitary opacities

High-resolution computerized tomography (HRCT) scans showing multifocal bronchiectasis and multiple small nodule

Bacteriologic (meeting one of the following criteria within one year) guidelines:

At least 2 culture-positive sputum samples

At least one culture-positive bronchial washing or lavage

Biopsy with histopathologic features consistent with mycobacterial infections and positive culture result

MANAGEMENT

MAC is not killed by any standard antituberculous drug except ethambutol at concentrations achievable in plasma. Yet, one half or more of MAC strains can be inhibited by achievable concentrations of rifabutin, rifampin, clofazimine, cycloserine, amikacin, ethionamide, ethambutol, azithromycin, clarithromycin, ciprofloxacin, SIn vivo data on microbiologic efficacy against MAC have been most **impressive with the new macrolides**, particularly clarithromycin. The focus of one multicenter, randomized, placebo-controlled trial was clarithromycin monotherapy, in dosages of 500, 1,000, and 2,000 mg, all twice daily, in patients with previously untreated disseminated MAC. The investigators reported a median >2 logs decrease in colony-forming units from blood culture specimens, representing a more potent microbiologic effect than had been reported in earlier treatment trials. This microbiologic effect was accompanied by significant clinical improvement in symptoms and quality-of-life indices.

Nonmacrolide antimycobacterial agents have been evaluated in several randomized, controlled trials. In one trial, investigators compared the microbiologic efficacy of 4-week monotherapy regimens of rifampin, ethambutol, or clofazimine in patients with previously untreated disseminated MAC. Results showed that only ethambutol effected a statistically significant reduction in blood MAC colony-forming units, suggesting that ethambutol might be the most potent of these 3 antimycobacterial agents. Data regarding rifabutin treatment for disseminated MAC also have been particularly promising.

Canadian HIV Trials Network study included 187 evaluable patients with MAC mycobacteremia who received randomized administration of a regimen of clarithromycin 1,000 mg twice daily, rifabutin 300-600 mg once daily, and ethambutol 15 mg/kg/day or a regimen of ciprofloxacin 750 mg twice daily, rifampin 600 mg once daily, clofazimine 100 mg once daily, and ethambutol 15 mg/kg/day.(11) The in vivo quantitative antimycobacterial effect was significantly better with the macrolide-containing regimen, as was median survival (8.6 vs 5.2 months;

p < .001).24

Treatment of pulmonary MAC infection in immunocompetent patients

ATS/IDSA guidelines recommend that most patients with nodular or bronchiectatic disease can be treated with a **thrice-weekly regimen** of clarithromycin 1000 mg or azithromycin 500 mg, rifampin 600 mg, and ethambutol 25 mg/kg. Therapy should be continued for **at least one year** after culture results revert to negative.**13** Patients with fibrocavitary lung disease or severe nodular or bronchiectatic disease should receive a daily regimen of clarithromycin 500–1000 mg or azithromycin 250-500 mg, rifampin 600 mg or rifabutin 150–300 mg, and ethambutol (15 mg/kg).

In addition, the ATS/IDSA guidelines suggest the addition of amikacin or streptomycin thrice weekly early in the course of treatment (initial 2-3 months) in patients with severe and extensive fibrocavitary lung disease. Fluoroquinolones can be used as a substitute for macrolides only if macrolides are not tolerated. The combination of a macrolide with a fluoroquinolone should be avoided, as they show antagonism in infections with some strains of MAC.

Treatment of disseminated MAC (DMAC) infection in patients with AIDS

Current guidelines recommend a combination of clarithromycin (500 mg twice daily) and ethambutol (15 mg/kg daily) with or without rifabutin (300 mg daily). Azithromycin (500-600 mg daily) can be substituted for clarithromycin.25 The addition of rifabutin has been recommended, especially in patients with advanced immunosuppression (CD4+ count <50 cells/μL), with high mycobacterial loads (>2 log colony-forming units/mL of blood)27, or in the absence of effective antiretroviral therapy. **Monotherapy should be avoided**, as it can lead to resistance.

Based on experience in patients without HIV infection, the guidelines suggest the use of amikacin or streptomycin as third or fourth drugs in these patients. The guidelines recommend continuing treatment until resolution of symptoms and reconstitution of cellular immunity (sustained CD4 counts >100 cells/μL for at least three months).

Fever should improve within 2-4 weeks of therapy initiation. If patients remain febrile for a longer duration than expected, repeat blood cultures and assess susceptibilities to antimicrobial agents. If the isolate is susceptible to a macrolide and the infection is not responding to therapy, consider adding other agents such as streptomycin or amikacin. If the MAC strain is resistant to macrolides, the macrolide can be replaced with a fluoroquinolone.

Since patients with MAC infection who are concomitantly receiving antiretroviral therapy may develop **immune reconstitution inflammatory syndrome (IRIS)26**, the guidelines suggest withholding antiretroviral therapy during the **first 2 weeks** of antimycobacterial treatment. However, if the patient is already receiving antiretroviral therapy, it should be continued. Patients with IRIS are generally treated with nonsteroidal anti-inflammatory drugs (NSAIDS) and, if necessary, with a short course (4-8 weeks) of systemic steroids such as prednisolone.

Addition of granulocyte macrophage colony-stimulating factor (GM-CSF) has been reported to be helpful in the treatment DMAC infection in patients with HIV/AIDS in whom traditional antimycobacterial therapy failed.

NOTE: Drug interactions are a major problem with rifabutin and clarithromycin. Higher doses of rifabutin (≥450 mg/day) are associated with higher rates of uveitis. The usual dose of rifabutin (300 mg/day) should be reduced by half (150 mg/day) if the patient is also receiving protease inhibitors.

MAC lymphadenitis

MAC lymphadenitis in children is treated with **surgical excision** of the affected lymph nodes, resulting in a cure rate that exceeds 90%. **Antibiotics are generally not required** but may be beneficial in patients with extensive lymphadenitis or with a poor response to surgical therapy. However, MAC lymphadenitis in immunocompromised patients, including patients with HIV infection/AIDS, generally responds to 6-12 months of antimycobacterial therapy and does not require surgery.

Hot-tub lung

The role of antimycobacterials and **corticosteroids** in the treatment of hypersensitivity pneumonitislike lung disease (hot-tub lung) due to MAC infection remains controversial. Patients with severe lung disease or respiratory failure should be treated with prednisolone tapered over 4-8 weeks. Immunocompromised patients and those with bronchiectasis also benefit from a short course (3-6 months) of anti-MAC treatment.

Crohn's disease

Clinical trials have failed to show any significant clinical benefit for antimycobacterial drugs used to treat Crohn's disease secondary to *M avium paratuberculosis.*

Chemoprophylaxis

Antimycobacterial prophylaxis is recommended in patients infected with HIV in whom the CD4+ lymphocyte count is **under 50 cells/μL**.The drug of choice is either clarithromycin 1000 mg/d or azithromycin 1200 mg/wk. Rifabutin 300 mg/d is an alternative to macrolides for MAC prophylaxis. However, rifabutin-associated drug interactions and complications (eg, uveitis) complicate the use of this agent**.**

IRIS

Development or worsening of symptoms soon after the initiation of HIV treatment (so-called **early or paradoxical reactions**). IRIS tends to occur more frequently in individuals receiving ART for the first time who experience a rapid decline in HIV viral load. It is recommended that patients presenting with presumed IRIS be treated on an individual basis with consideration of the use of **nonsteroidal antiinflammatory drugs (NSAIDs) or steroids**.

Complications

Patients with AIDS and disseminated MAC (DMAC) infection may develop anemia or weight loss, or they may die, if untreated. Untreated patients with significant lung disease may develop respiratory insufficiency or weight loss. Severe disability or death may result from respiratory failure.

Prognosis

Before the era of effective antiretroviral treatment, the life expectancy among patients with AIDS and MAC infection was 9 months.However those receiving antiretroviral therapy and anti-MAC treatment have a relatively better prognosis.

Patients with lung disease and pulmonary MAC infections with focal nodules usually have a benign course. Patients with more extensive disease have a 90% chance of recovery and a 20% chance of relapse after treatment with anti-MAC drugs.

DIFFERENTIAL DIAGNOSIS

Following conditions are to be considered in differential diagnosis of MAC infection:-

Aspergillosis,B-CellLymphoma,Bartonellosis,Mediastinal Lymphoma,Benign Lung Tumors,

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Non-Hodgkin Lymphoma,Blastomycosis,MycobacteriumKansasii ,Catscratch Disease,

Nontuberculous mycobacterial infections,Coccidioidomycosis (Infectious Diseases)

Aspiration Pneumonia,Cryptococcosis,Pneumonia,Bacterial,Cyto megalovirus,

Fungal Pneumonia,Fever of Unknown Origin,Sarcoidosis,Histopl asmosis,Toxoplasmosis,

Hypersensitivity Pneumonitis,Tuberculosis,Infectious Mononucleosis,

Wegener Granulomatosis,Non-Small Cell Lung Cancer,Oat Cell (Small Cell) Lung Cancer

MEDICAL PITFALLS

Macrolides are likely to interact with drugs metabolized in the liver.

Ethambutol may cause optic neuritis and blindness, especially in patients with coexisting renal dysfunction.

Rifampin and rifabutin may decrease the effectiveness of contraceptives and other drugs metabolized in the liver

Advise patients of this potential effect. Rifabutin is also known to cause uveitis, for which patients need regular eye examinations.

Failing to offer prophylaxis to patients with HIV with a CD4+ lymphocyte count of below 50 cells/μL may lead to development of disseminated *M avium* complex (DMAC) infection

Patient Education

Advise patients that antimycobacterial therapy alone will not eradicate MAC infection, but should decrease symptoms and improve quality of life**. A response to treatment may take up to 4 weeks**. If medications are discontinued, the disease almost always recurs, unless the CD4 count has increased to >50-100 cells/μL in response to ART.

Patients must take all medicines exactly as prescribed. If doses are missed, or if the medication is stopped and restarted, *Mycobacterium* can develop resistance to the medications. If patients are having trouble taking the medications on schedule, they should contact their health care providers immediately.

Educate patients about the benefits of ART in strengthening the immune system and preventing opportunistic infections such as DMAC.

Urge patients to contact the clinic immediately if they notice worsening symptoms, or new symptoms. DMAC is an opportunistic infection of late-stage HIV and indicates profound immune suppression. Some patients may not respond to MAC treatment or to ART. Because this is a life-threatening disease, clinicians should discuss advance directives and durable power of attorney with patients. Referral to a social worker, mental health clinician, or chaplain experienced in such issues may facilitate this discussion.

Summary Recommendations

The advent of antimycobacterial macrolide therapy has greatly improved both prophylaxis and treatment of disseminated MAC infection. Although questions remain about which particular regimens are optimal, several general recommendations can be made.

Suspect disseminated MAC in patients with CD4 <50 cells/μL and nonspecific symptoms, signs, and laboratory abnormalities.

Mycobacterial culture of peripheral blood is a sensitive method for diagnosing disseminated MAC. A single blood culture identifies 91% and 2 cultures identify 98% of cases of MAC bacteremia. Stains and culture biopsies from other normally sterile body sites (eg, bone marrow, lymph node, or liver) also may be useful.

Patients with CD4 counts <50 cells/μL who exhibit no clinical evidence of active mycobacterial disease should receive prophylaxis with either clarithromycin (500 mg twice daily) or azithromycin (1,200 mg weekly); the latter could be coadministered with 300 mg rifabutin daily. MAC prophylaxis should be discontinued in adult patients without a history of MAC disease whose CD4 counts remain >100 cells/μL for at least 3 months on ART.

Optimal treatment should begin with clarithromycin (500 mg twice daily) plus ethambutol (approximately 15 mg/kg/day). Rifabutin may be added to this regimen, but the exact rifabutin dosing depends on other concomitant medications that might result in drug interactions. Three-drug anti-MAC therapy is preferred for individuals who do not plan to start or cannot be prescribed an effective antiretroviral regimen.

It appears **safe to withdraw primary and secondary** prophylaxis in patients who have sustained CD4 counts >100 cells/μL for at least 3-6 months on ART. Prophylaxis should be reinitiated if the CD4 T-cell count declines.

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