



## Nontuberculous mycobacteria in the HIV infected patient

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Disseminated *Mycobacterium avium* complex (MAC) disease was one of the first opportunistic infections recognized as part of the syndrome of AIDS 20 years ago [1]. Clinicians rapidly became familiar with the classic triad of fever; drenching sweats, and anorexia characteristic of this previously obscure disease [1–3]. Interest in disseminated MAC and nontuberculous mycobacteria (NTM) infections increased as a result of the HIV epidemic, and therapeutic strategies to treat and prevent these diseases evolved over the next 15 years [4–6]. Prevention and treatment regimens were lifelong because cure of NTM was not achievable in AIDS patients with profound immune suppression.

The application of highly active antiretroviral therapy (HAART) for the treatment of HIV disease dramatically reduced rates of all opportunistic infections including NTM [7,8]. Despite this decline, NTM remains one of the most commonly encountered opportunistic infections in AIDS patients [8]. Disease resulting from NTM now occurs in the following settings: in patients not receiving antiretroviral therapy, in patients who are intolerant or failing antiretroviral therapy, and in the early period following the initiation of HAART prior to immune recovery. HAART also altered the clinical approach to MAC and led to the recognition of new clinical syndromes.

In this article, we address the changing epidemiology of NTM, new approaches to prophylaxis and treatment, and the newly described “immune reconstitution syndrome” associated with NTM.

### **Mycobacterium avium complex**

The *Mycobacterium avium* complex includes both *M avium* and *M intracellulare*, which together account for the majority of disease-causing species of NTM in the HIV-infected patient. *M avium* is the most common cause of NTM disease in patients with AIDS, with serotypes 1, 4, and 8 being the most commonly isolated [10,11]. Although there is a geographic variation in serotypes within the United States, MAC disease occurs in all demographic groups and its occurrence is not influenced by gender or HIV risk factors [12,13].

### *Clinical perspective on the epidemiology of MAC*

MAC is environmentally acquired and is not transmitted from human to human. MAC can be recovered from numerous environmental sources including water, soil, food, and animals; however, it is not clear which source or sources are principally responsible for human infection [13,14]. The presence of MAC in the sputum or stool of patients with AIDS prior to the development of disseminated disease suggests that infection results from inhalation or ingestion [10,15,16].

Profound immunocompromise is the major risk for the development of disseminated MAC [17]. A number of studies demonstrate that the median CD4 cell count is consistently less than 50 cells/mm<sup>3</sup> at the time that disseminated disease is diagnosed. In one prospective observational study of HIV-infected patients cultured monthly for MAC, the incidence of infection for patients with less than 200 CD4 cells/mm<sup>3</sup> was 43% after 2 years. In the subgroup of

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patients with less than 10 CD4 cells/mm<sup>3</sup>, the incidence of infection was 39% at 1 year [18]. Another risk factor for MAC is increased HIV RNA levels. Williams et al showed that plasma HIV RNA level greater than 100,000 copies/ml was associated with a threefold increase in the risk of developing MAC in patients with CD4 < 75 cells/mm<sup>3</sup> [19].

Other risk factors for the development of disseminated MAC appearing in the literature include exposure to hard cheeses and residence in the southern states; however, the inability to culture MAC from cheese and the geographic differences in the approach to diagnosis have brought both these associations into question [20].

One of the interesting observations of NTM disease in HIV-infected patients is the low frequency of disease in Africa despite the presence of NTM in the environment. Evidence of environmental exposure to MAC occurring in humans in Africa is supported by the finding that skin test reactivity to *M avium* is as common in Kenya as it is in certain areas of the United States [10]. A number of explanations have been put forth to explain this observation. Comorbidities may result in death prior to progression of HIV disease to a state of immune compromise that is associated with NTM disease. Another theory put forth to explain the low incidence of disease is that exposure to other mycobacterial pathogens such as *M tuberculosis* or *M bovis* (in bacillus Calmette-guerin [BCG]) provides cross-protective immunity to MAC. This theory is supported by the low reported incidence of disease in countries such as Sweden, where childhood vaccination with BCG was common [21–23].

The literature is not conclusive in terms of explaining this NTM epidemiology in Africa. As prophylaxis for opportunistic infections in Africa is increasingly implemented, we may also observe increases in NTM disease.

The most important change in the epidemiology of NTM has been the tremendous reduction in new cases. Disseminated MAC steadily declined over the past decade with the most rapid decline occurring after the introduction of HAART. Data from the Adult/Adolescent spectrum of HIV disease project group showed a decline in the incidence of MAC of 39.9% per year from 1996 to 1998. Palella and colleagues described a similar decline in a cohort of 1255 patients from 1994 to 1995 [7,8]. Other factors partially responsible for the decline in NTM are the improved general care of HIV infected patients and specific preventative measures for opportunistic infections [24]. Most cases of MAC today occur in patients who have not accessed care; however, it is possible that we may see an increase in

the incidence in those patients failing antiretroviral therapy [25].

#### *Pathogenesis in HIV-infected patients*

Disseminated MAC is most likely a result of primary infection rather than reactivation. In vitro evidence showing that MAC can bind and invade intestinal cell lines supports the animal models showing that colonization of the gastrointestinal or respiratory tracts precedes disseminated disease [15]. The precise immune defect predisposing HIV infected patients to disseminated disease is unknown. In vitro, cells from HIV infected patients are able to ingest *M avium* and respond to interferon gamma [26]. Reduction in host production of cytokines, such as interferon gamma, increased production of *M avium* growth promoting cytokines, such as interleukin (IL)-6, may favor dissemination of NTM in HIV infection [27,28].

The propensity for developing disseminated NTM disease in HIV infected patients is dependent not only on the level of the host's immunity but also on the virulence of the organism. Support for this is found in the increased isolation of certain serotypes in disseminated disease and the fact that transfection of a plasmid into a nonplasmid-containing strain of *M avium* is associated with increased intracellular replication [29,30]. Intracellular survival of *M avium* is enhanced by inhibition of phagosome-lysosome fusion, and localization of the organism to less acidic vacuoles within the cell favors long-term survival [31].

Similar to other opportunistic infections, the development of MAC is associated with a more rapid progression of HIV disease and subsequent death. Many opportunistic infections, including disseminated *M avium*, activate lymphocytes. Because productive HIV infection requires cellular activation, HIV replication increases when an opportunistic infection develops. In one study, HIV RNA plasma levels increased after the onset of disseminated MAC [32]. Increased HIV replication within macrophages has also been reported in patients with disseminated disease [33].

#### *Clinical manifestations*

AIDS patients not receiving HAART who become infected with MAC differ from immunocompetent hosts in that they tend to develop disseminated disease. The most commonly encountered symptoms include fever, night sweats, anorexia, and weight loss (Table 1). Nausea, vomiting, diarrhea (47%), and

Table 1  
Frequency of symptoms, physical findings, and laboratory abnormalities among patients with disseminated MAC<sup>a</sup>

Findings	No. of patients evaluated	Percentage of positive patients
Fever	120	87
Night sweats	85	78
Diarrhea	92	47
Abdominal pain	54	35
Nausea/vomiting	31	26
Weight loss	37	38
Lymphadenopathy	54	37
Intra-abdominal		
Mediastinal	49	10
lymphadenopathy		
Hepatosplenomegaly	38	24
Anemia (<8.5 g/dL)	39	85
Elevated serum alkaline phosphatase	38	53

<sup>a</sup> From Benson CA, Ellner JJ. Mycobacterium avium complex infection and AIDS: advances in theory and practice. Clin Infect Dis 1993;17:7–20.

abdominal pain (35%) are other frequently reported symptoms. These symptoms, although classic for MAC are nonspecific, and investigations for other AIDS complications such as tuberculosis, fungal infections, and malignancies are routinely performed [11].

Because of the widespread involvement of the reticuloendothelial system, physical exam often reveals hepatomegaly, splenomegaly and lymphadenopathy. Anemia and an elevated alkaline phosphatase are among the more commonly reported laboratory abnormalities [34].

Localized forms of infection are reported in patients with AIDS and include osteomyelitis, pancreatitis, and meningoencephalitis, as well as intra-abdominal and soft-tissue abscesses [11].

Pulmonary disease occurs in fewer than 5% of cases of disseminated disease and may occur without evidence of dissemination. In the immunosuppressed host, pulmonary infection has a myriad of radiographic presentations including nodules, infiltrates (diffuse or localized), cavities, and lymphadenopathy [35,36]. A recent series from northern Australia suggested that the incidence of pulmonary MAC might be higher than this, with 4 out of 15 of their HIV-infected patients developing pulmonary manifestations [37].

Recently, a new clinical entity caused by *M avium* has been described in patients with AIDS who initiate potent antiretroviral therapy. This entity probably represents a recovery in pathogen-specific immune responses to infections that are already present but not clinically detectable [9]. A number of different names have been coined for this syndrome: immune reconstitution syndrome, immune recovery disease, and the paradoxical response. This syndrome has been described in a number of infections including *M tuberculosis*, cytomegalovirus, hepatitis B and C, cryptococcosis, and MAC [9,38,39].

When this syndrome occurs as a result of MAC, the presenting features are usually fever, lymphadenitis (mesenteric and/or cervical), and leukocytosis. The disease present, however, with symptoms related to any site where the infection has remained quiescent in the absence of an adequate immune response (Fig. 1).

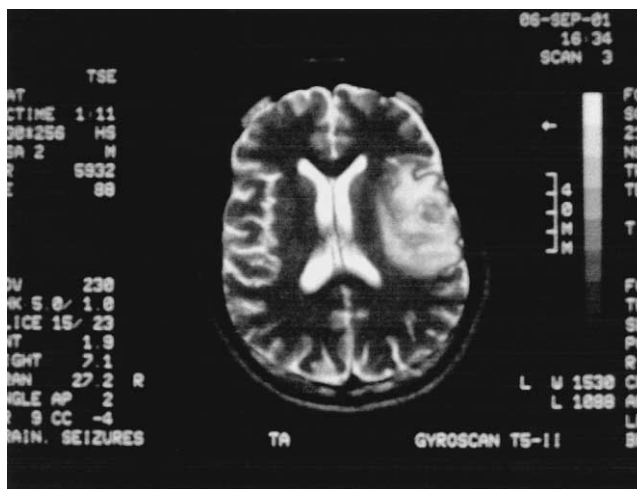


Fig. 1. MR imaging shows localized *Mycobacterium avium* complex lesion related to immune reconstitution.

The symptoms are often fairly mild and in most cases will resolve with continued antiretroviral therapy. Interestingly, blood cultures are usually negative for MAC. Should the inflammatory symptoms be severe, a short course of corticosteroids may be necessary.

The onset of the immune reconstitution syndrome usually occurs within the first few weeks following the initiation of potent antiretroviral therapy; however, its onset may be delayed for up to 1 year [40]. Although this syndrome is usually seen when HAART is first initiated, it can occur each time the patient is challenged with HAART.

It has been suggested by some that there may be a genetic predisposition to the development of the immune reconstitution syndrome. Price et al showed that HLA B44 was associated with the development of atypical cytomegalovirus (CMV) retinitis following the initiation of HAART [41].

### Diagnosis

Colonization with MAC has been described in both the immunocompromized as well as the immunocompetent patient. It is therefore important that certain diagnostic criteria are met before disease is attributed to infection with MAC [12,42].

Isolation of the organism from a normally sterile site is often sufficient to make the diagnosis; with blood cultures remaining one of the easiest and most sensitive methods of diagnosing disseminated disease. A single blood culture is reported to have a sensitivity of 90–95%. In rare cases where the clinical suspicion is high and blood cultures are negative, liver or bone marrow biopsy should be considered [10,42].

A number of different culture mediums are available, the Lowenstein-Jensen being the most commonly used solid medium. Broth media allow for the more rapid detection of mycobacteria, usually within half the time it takes using a solid medium. Detection of mycobacteria in broth media, such as the BACTEC or Septi-check system, is dependent on the production of CO<sub>2</sub> which is then detected radiometrically [43].

Mycobacterial detection using various DNA probes has been a major advance over the past decade. A variety of probes are commercially available. These DNA probes will detect numerous mycobacteria within a few hours of adequate growth in a culture medium [44,45].

In AIDS patients, MAC is often detected in the respiratory tract, although this finding does not necessarily indicate disseminated infection or the need for treatment. A thorough search for other

pathogens should be pursued before the diagnosis of pulmonary MAC is made. Distinguishing MAC and other tuberculous infections on a clinical basis is very difficult because of the nonspecificity of clinical findings. Rapid diagnostic testing for *M tuberculosis* can be very helpful when a patient has acid-fast bacilli seen on smear.

The American Thoracic Society has provided guidelines for the diagnosis of MAC-related pulmonary disease. These guidelines are recommended for both HIV and non-HIV infected patients [46].

### Treatment

For the clinician treating disseminated MAC, there are a number of different combinations available for treatment; however, several principles of therapy should be observed. First, the cornerstone of treatment is the inclusion of either clarithromycin or azithromycin in the regimen. As single agents, these drugs are the most potent drugs available for the treatment of MAC. The second principle is that treatment regimens should contain at least one additional agent to prevent the development of resistance. Third, patients failing treatment should be tested for drug resistance, with therapy adjusted accordingly [5,47]. In vitro assays of drug susceptibility provide useful information for clarithromycin and azithromycin; cutoffs for other drugs are less clear. Finally, in the absence of immune recovery (treatment of HIV disease with HAART) treatment of MAC should be life-long [48].

Clarithromycin is the macrolide most often used to treat MAC and should be prescribed at a dose of 1000 mg per day. Although higher doses result in a more rapid clearance of bacteremia, they also have been reported to cause more side effects and (possibly) a higher mortality [5]. Azithromycin is a comparable alternative to clarithromycin and should be given at a dose of 600 mg/day. Dunne et al recently showed that azithromycin, when given at 600mg per day, is as effective as clarithromycin dosed at 500 mg bid [49]. Tolerability is important for patient adherence, and physicians should not hesitate to use these agents interchangeably to achieve maximal effect.

Ethambutol has been shown to reduce the relapse of bacteremia when given to patients on a clarithromycin-containing regimen; hence, its choice as the second agent in the treatment of disseminated MAC [50,51]. Whether a third agent should be added for the treatment of disseminated MAC is still open to debate. Gordin et al recently showed in a study of 178 patients that there was no impact on bacterio-

logic response or survival when rifabutin was added to clarithromycin and ethambutol [52]. There was, however, a trend to a lower incidence of resistance in the rifabutin group.

Agents less studied include the quinolones, cycloserine, amikacin, and ethionamide. Clofazimine is no longer recommended for the treatment of disseminated MAC. This is based on a study showing that when clofazimine was added to clarithromycin and ethambutol, there was no increase in efficacy and a higher mortality [53].

Recurrence of bacteremia in a patient on an effective multidrug regimen should prompt clarithromycin and azithromycin susceptibility testing, and in those patients showing resistance, two new agents should be added [5]. Macrolide therapy should be continued, using the principle that most patients will have a mixed infection with some sensitive strains remaining [54]. In patients failing MAC therapy with resistant organisms, optimizing HIV therapy may offer the best chance of controlling or curing the infection.

With the many benefits of antiretroviral therapy comes the risk of drug interactions. Rifabutin, a drug often used to treat MAC interacts with many of the drugs used to treat HIV infection. The clinician should be aware of the potential interactions between the antibiotics and antiretroviral agents, as outlined in Table 2 below.

The duration of MAC therapy in patients who are responding to HAART is not known. In one recent observational study, Aberg described 4 patients who had their antimycobacterial therapy discontinued. All four patients had responded to HAART with absolute CD4 cell counts  $>100$  cells/mm<sup>3</sup> and viral loads  $<1,000$  copies/mL, and all patients had received more than 12 months of antimycobacterial therapy. After follow-up (range of 8–13 months), all patients remained asymptomatic with negative blood cultures [55].

### Prophylaxis

MAC prophylaxis should be initiated in patients at high risk for MAC in whom disseminated disease is not present. If rifabutin is required, active tuberculosis should be excluded before this drug is initiated.

The United States Public Health Service/Infectious Diseases Society of America (USPHS/IDSA) guidelines advise that all patients who are HIV infected with CD4 counts  $<50$  cells/mm<sup>3</sup> receive preventative therapy for disseminated MAC [48].

The most commonly used regimens are azithromycin 1200 mg once weekly or clarithromycin 500 mg twice daily. Both agents reduce the incidence

of MAC bacteremia by approximately 60% when compared with placebo [56,57].

Although inferior to azithromycin or clarithromycin, rifabutin is acceptable when these drugs are contraindicated. Rifabutin alone reduces the risk of bacteremia by approximately 50% [58].

The combination of rifabutin with the macrolides was studied as a possible means of improving prophylaxis; this combination resulted, however, in an increase in adverse events, an increase in drug interactions, and no survival advantage. Combination therapy can therefore not be recommended for MAC prophylaxis [59].

Despite the proven effectiveness, prescription of acceptable MAC prophylaxis remains suboptimal. The Centers for Disease Control and prevention through the ASD project showed that, by the end of 1998, only 54% of eligible persons were prescribed prophylaxis [8].

Based on information obtained from two large clinical trials, the 2001 USPHS/IDSA guidelines recommend that primary prophylaxis be discontinued in patients who have responded to antiretroviral therapy and have sustained a CD4 T lymphocyte count of greater than 100 cells/mm<sup>3</sup> for at least 3 months [48,60,61]. Although the CD4 count is the most important variable when considering stopping prophylaxis, other risk factors that should be considered are

Table 2<sup>a</sup>

Suggested Rifabutin dosage adjustment for anti-retroviral therapy

Drugs interacting with Rifabutin	Alteration in the dose of Rifabutin from 300 mg daily
Protease inhibitors	
Saquinavir	No change required
Nelfinivir	Decrease to 150 mg daily
Indinavir <sup>b</sup>	
Amprenavir	
Ritonavir	Decrease to 150 mg twice weekly
Lopinavir ritonavir	
NNRTIS	
Delavirdine	Avoid concomitant use
Nevirapine	No change needed
Efavirenz	Increase to 450 mg

NNRTIS, non-nucleoside reverse transcriptase inhibitor.

<sup>a</sup> USPHS/IDSA. 2001 USPHS/IDSA guidelines for the prevention and treatment of opportunistic infections in persons infected with human immunodeficiency virus, revision 13. 2001, p. 1–64.

<sup>b</sup> In addition to the suggested changes to Rifabutin dosing, the USPHS/IDSA guidelines suggest increasing Indinavir dosing to 1000 mg q8h when these 2 agents are used together.

the current viral load and the CD4 nadir. Patient compliance with continued antiretroviral therapy as well as the availability of an effective treatment regimen should also weigh in the decision of whether or not to stop prophylaxis.

### **Nontuberculous mycobacteria other than MAC**

Most NTM disease in HIV-infected patients other than MAC is caused by *M kansasii* [62]. Some of the other NTM encountered in HIV-infected patients include *M chelonae*, *M fortuitum*, *M gordonae*, *M malmoense*, *M marimum* and *M xenopi*. All of these organisms are capable of causing disseminated disease with a symptom complex resembling MAC [10].

These organisms are often contaminants or colonizers; however, when the typical symptoms are present, isolation of one of these organisms from a normally sterile site provides strong evidence for a true infection.

#### ***M kansasii***

*M kansasii* is the second most common cause of nontuberculous pulmonary disease in the United States and causes a clinical and radiographic picture that closely resembles *M tuberculosis* [62]. Despite this similarity, there is little evidence of human-to-human transmission. The source of infection remains unclear, although the presence of the organism in tap water has been well documented [63].

*M kansasii* infection usually occurs in severely immunosuppressed patients (CD4 counts >50 cells/mm<sup>3</sup>) and typically presents with isolated pulmonary disease ( $\pm$  70%). Disseminated disease is less common than that seen in MAC, with only approximately 20% having only extrapulmonary manifestations. Those with disseminated disease were typically the most severely immunocompromised [10].

#### *Clinical presentation*

Symptoms seen in *M kansasii* infections are usually those encountered in patients with tuberculosis and include fever, cough, night sweats, and weight loss. Chest pain and hemoptysis are less common than in tuberculosis. In addition to those symptoms mentioned, disseminated disease often features lymphadenopathy, hepatosplenomegaly, osteomyelitis, and cutaneous lesions [64].

#### *Radiographic findings*

Radiographically, the disease is most often seen in the upper lobes and manifests as multiple cavities of varying sizes with associated volume loss. Disease is most often unilateral, with bilateral disease reported in approximately 40% of cases [62,63].

Although it is almost impossible to distinguish *M kansasii* from *M tuberculosis* on the chest radiograph, some features suggestive that *M kansasii* is the responsible organism include thin walled cavities, smaller cavities, and a higher incidence of pre-existing lung disease.

#### *Diagnosis*

The diagnosis of *M kansasii* requires either the isolation of the organism from a sterile site or, in the case of pulmonary disease, the American Thoracic Society (ATS) criteria should be met. These are the same criteria that were outlined earlier for the diagnosis of MAC-related pulmonary disease [46].

DNA probe technology was initially thought to be a poor tool for the identification of *M kansasii*. It was the failure of the earlier probes to identify all groups within the *M kansasii* species that led to false negatives and, hence, this opinion. Reformulated versions of Accuprobe (Gen Probe Inc, San Diego, CA) have overcome this problem and are now widely used for the identification of *M kansasii* [65,66].

#### *Treatment*

The ATS recommends a combination of isoniazid (INH), rifampin, and ethambutol for a period of 18 months or until the cultures have been negative for a minimum of 12 months [46]. Pyrazinamide (PZA) should be avoided because of widespread resistance of the organism; INH on the other hand can often be used despite resistance on susceptibility testing. The reason for this is that many isolates are resistant at concentrations of 1 $\mu$ g/mL but sensitive at concentrations of 5 $\mu$ g/mL which are similar to those found in vivo [10].

Other agents with activity against *M kansasii* include streptomycin, clarithromycin, sulfamethoxazole, and certain quinolones.

#### ***M gordonae***

*M gordonae* is a ubiquitous organism and is usually considered a contaminant when recovered in culture. Although considered to be an organism with low pathogenicity, there have been reports of both

pulmonary and disseminated disease in the immunocompromised host [67].

Relating disease to *M. gordonae* requires that the same criteria be met as for other NTM.

The pulmonary presentation of *M. gordonae* does not appear to have any typical presentation; a recent study of 19 patients all with sputum positive for *M. gordonae* failed to show any typical radiographic features [68]. Although the clinician is often unable to distinguish the type of NTM from the chest radiograph, the finding most commonly noted in AIDS patients with NTM (excluding *M. kansasii*) is an interstitial pattern that may be localized or diffuse. Cavitory disease has been reported to be very rare in this immunosuppressed population. The treatment usually requires a multidrug regimen with rifampin and ethambutol making up the core of the regimen.

### *M. genavense*

*M. genavense* is a newly recognized pathogen in HIV-infected patients. It was first described in a patient with AIDS in 1990 [69]. Its incidence is probably similar to other NTM with Monill et al reporting 8 cases of *M. genavense* over a 5-year period, with these cases comprising 9% of the NTM infections in their institution [70]. Some investigators have suggested that the true prevalence may be underestimated because of difficulties experienced when culturing the organism.

Patients infected with *M. genavense* are usually severely immunocompromised (average CD4 count of 50 cells/mm<sup>3</sup>) and present with nonspecific symptoms of fever, wasting, abdominal pain, and diarrhea. Physical findings include hepatosplenomegaly, anemia, and abdominal lymphadenopathy. Pulmonary involvement is rare, if it exists at all.

The findings on abdominal CT scan are also nonspecific with lymphadenopathy (retroperitoneal, mesenteric, and peri-pancreatic), splenomegaly and diffuse proximal small bowel thickening being the most well-described features [70].

Treatment has not been well studied, although success with macrolide-based regimens similar to those used for MAC has been reported [10].

### *M. xenopi*

*M. xenopi* is a commonly found organism and is often considered a contaminant. Reports of an increasing incidence are probably the result of more sensitive tests becoming available. In a recent series

from Bellevue Hospital, they reported that, following the introduction of the MGIT (mycobacterial growth indication tube) system, the number of isolated cases increased from 12 cases in the 4 years prior to the introduction of the system to 381 cases in the 4 years following the introduction [71].

The clinical features of *M. xenopi* infection in the HIV-infected patient include both disseminated disease and pulmonary manifestations. Pulmonary disease typically occurs in those with pre-existing pulmonary disease.

The treatment usually includes a combination of INH, rifampin, ethambutol, and streptomycin. In a study of non-HIV infected patients, the addition of INH to a regimen of rifampin and ethambutol resulted in lower relapse rates and less treatment failure [72].

### Other mycobacteria

A number of other mycobacteria have been reported to cause disease in the HIV-infected patient. Many of the clinical syndromes are similar to those seen with MAC and can only be differentiated by identification of the organism

### Summary

The reduction in disseminated NTM infections caused by HAART is one of the success stories in the history of HIV in the developed world. Despite this success, these diseases still occur and may have atypical presentations in patients receiving HAART. Clinicians treating HIV-infected patients must remain familiar with the diagnosis and treatment of these diseases and implement prevention strategies when indicated.

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