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# Disseminated *Mycobacterium avium* on HIV/AIDS: Historical and Current Literature Review

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## Abstract

**Combination antiretroviral therapy (cART) has changed *Mycobacterium avium* epidemiology. A significant decrease in the incidence of disseminated *M. avium* complex (DMAC) infection was observed between pre-cART and post-cART periods. In contrast, diagnoses of DMAC more than doubled from 1990 to 1996. During this time, DMAC prevalence in people living with AIDS (PLHA) in developed countries reached 20-23% overall and >40% in groups with CD4 cell counts <10 cells/mm<sup>3</sup>. At present, DMAC in PLHA has an incidence of two events per 1000 patient years. Recently, the centers for disease control changed the criteria for MAC primary prophylaxis, where only patients without immediate cART and CD4 cell counts <50 cells/mm<sup>3</sup> are prescribed 1200 mg of azithromycin weekly. Treatment is discontinued when patients initiate effective cART. Diagnosing a disseminated *M. avium* infection is difficult due to the low accuracy of fluid cultures and a lack of diagnostic processes. However, the usefulness of newer molecular techniques such as whole-genome sequencing has not been evaluated for DMAC and HIV/AIDS. As DMAC has a high mortality rate if not properly diagnosed and treated, we performed a literature review of HIV/AIDS and DMAC epidemiology, risk factors, prophylaxis, clinical manifestation, diagnosis, prognosis, and treatment. (AIDS Rev. 2020;22:1-7)**

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## Key words

***Mycobacterium avium*. Disseminated *Mycobacterium avium*. Opportunistic infection. HIV. AIDS.**

## Background

*Mycobacterium avium* complex (MAC) has been associated with HIV/AIDS for 1982, and in 1987, became an AIDS-defining illness<sup>1,2</sup>. Divergence from the *M. avium* epidemiological scenario was demonstrated in 1986 when it was frequently found in developed countries as the most common nontuberculous *Mycobacterium* (NTM) in the context of AIDS<sup>3,4</sup>. Patients

with disseminated MAC (DMAC) infections were usually extremely immunosuppressed and had a poor prognosis, and the incidence of DMAC among people living with AIDS (PLHA) reached 20%<sup>4,5</sup>. Combination antiretroviral therapy (cART) changed this scenario, and a significant decrease in DMAC incidence occurred between pre-cART and post-cART periods<sup>6,7</sup>. At present, the incidence of DMAC infections in PLHA is two events per 1000 patient years<sup>7</sup>.

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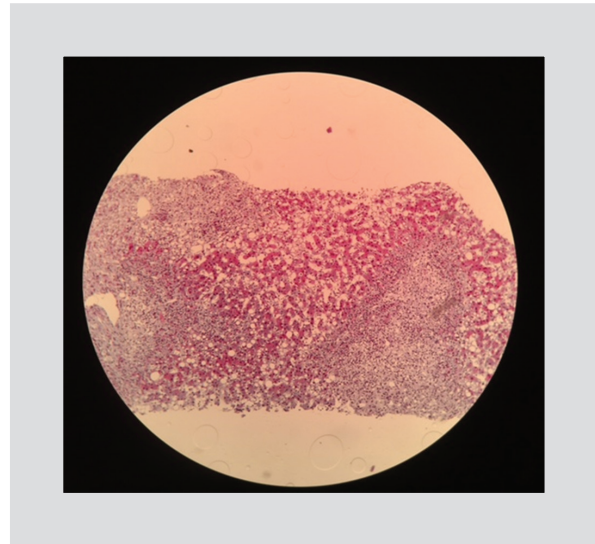
Diagnosing a disseminated *Mycobacterium* spp. infection is difficult, due to the low accuracy of fluid cultures and a lack of diagnostic processes. Although blood or bone marrow cultures and bone marrow biopsies yield better results than samples from other tissues<sup>8-10</sup>, the typical time to detect *Mycobacterium* spp. on cultures is 10-15 days. Polymerase chain reaction (PCR) can be performed for the urine, or blood can be an option if samples are available<sup>11</sup>.

We performed a literature review in PubMed, LILACS, the Web of Science, and SciELO on DMAC and HIV/AIDS epidemiology, risk factors, prophylaxis, clinical manifestation, diagnosis, prognosis, and treatment. In addition, we report two cases of DMAC infection in PLHA that presented as liver failure diagnosed only by a liver biopsy to better demonstrate disease complexity. The Ethical Committee of the Emilio Ribas Institute of Infectious Diseases approved these case reports.

## Illustrative case reports

### Case 1

A 43-year-old woman diagnosed with HIV/AIDS with poor adherence to cART (tenofovir, lamivudine, and atazanavir plus ritonavir) presented at the clinic complaining of dysuria, fever, night sweats, weight loss, abdominal pain, nausea plus vomiting, jaundice, and acholic feces for 20 days. A week before, she was treated for cystitis with ciprofloxacin. Physical examination revealed dehydration, jaundice, and tender abdomen, mainly in the right upper quadrant (negative Blumberg sign and negative Murphy sign), palpable liver 5 cm below the right costal margin, and palpable spleen 5 cm below the left costal margin. Abdominal computed tomography (CT) showed hepatosplenomegaly, low-attenuation spleen lesions compatible with splenic abscesses, enlarged perihepatic and retroperitoneal lymph nodes, and slight dilatation of the common bile duct. Complete blood cell counts revealed anemia (hemoglobin [Hb] 7.5 mg/dL) and thrombocytopenia (87,000 cells/mm<sup>3</sup>). Liver function tests were also altered: direct bilirubin 15.4 g/dL, indirect bilirubin 5.6 mg/dL, and international normalized ratio (INR) 1.70. The patient presented with severe hepatic and hematological dysfunction, with hepatosplenomegaly, lymphadenomegaly, and possible splenic infarcts or abscesses. Blood cultures for mycobacteria, fungi, and aerobic bacteria were negative. Bone marrow aspirate, biopsy, and culture results were

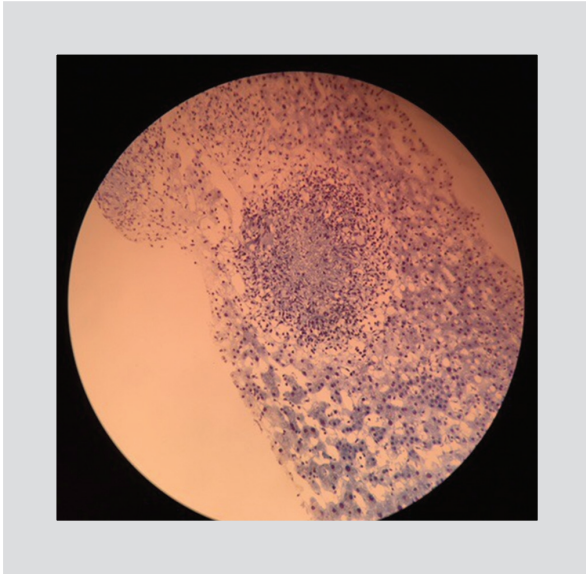


**Figure 1.** Biopsy of granulomatous infiltrate in hepatic parenchyma.

normal. The CD4 cell count was 163 cells/mm<sup>3</sup>, and the HIV viral load was 200,000 copies/mm<sup>3</sup>. Liver biopsy revealed a caseous granuloma (Fig. 1). Disseminated *Mycobacterium* spp. infection was suspected, and treatment with rifabutin, pyrazinamide, isoniazid, ethambutol, and clarithromycin was started. A week later, urine cultures were positive for the presence of MAC. The dosage of clarithromycin and ethambutol was adjusted, and after 2 weeks, the patient's clinical status improved.

### Case 2

A 30-year-old man diagnosed with HIV/AIDS with irregular treatment (tenofovir, lamivudine, and efavirenz) presented at the clinic complaining of liquid diarrhea (six episodes a day) without dysenteric symptoms such as blood or mucus. The patient also had a fever (38.4°C) and jaundice and had lost 10 kg in 20 days. Physical examination revealed dehydration, jaundice, and a diffuse painful abdomen. Physical examination revealed the following: negative Blumberg sign, negative Murphy sign, palpable liver 7.5 cm below the right costal margin, palpable spleen 7.5 cm below the left costal margin, and no sign of abnormal pulmonary or cardiovascular function. Abdominal CT demonstrated hepatosplenomegaly, enlarged perihepatic and retroperitoneal lymph nodes, and moderate ascites. Anemia (Hb 5 mg/dL), leukopenia (1800 cells/mm<sup>3</sup>), and thrombocytopenia (49,000 cells/mm<sup>3</sup>) were found. Liver function tests were also altered: total bilirubin 6.1 mg/dL and INR 1.78. The patient progressed to septic shock, and vasopressors were administered. The lymphocyte



**Figure 2.** Biopsy of granulomatous infiltrate in hepatic parenchyma.

CD4 cell count was 61 cells/mm<sup>3</sup>, and the HIV viral load was 300,000 copies/mm<sup>3</sup>. An etiological investigation was attempted with aerobic, anaerobic, fungus, and mycobacteria blood culture in addition to *Cytomegalovirus* blood PCR and protozoan and parasitological tests. All results were negative. Bone marrow biopsy revealed diffuse hypocellularity, but cultures were negative. A liver biopsy was attempted after platelet transfusion and revealed a caseous granuloma (Fig. 2), but the culture was negative. Disseminated *Mycobacterium* infection was suspected and the treatment with rifabutin, pyrazinamide, isoniazid, ethambutol, and clarithromycin was started. After 12 days of treatment, the patient presented without cholestasis in a laboratory examination, showed clinical improvement, and was discharged from the hospital. Although DMAC infection was not shown in this case, an aggressive *Mycobacterium* spp. treatment (DMAC and *Mycobacterium tuberculosis*) was warranted, which demonstrates the diagnostic difficulties associated with this disease in lower resource settings.

## Literature review

In the post-cART era, DMAC infections in PLHA have become a rare diagnosis, even in developed countries, where the incidence was previously much higher than in low- and middle-income countries. Here, we report on two DMAC cases marked by liver failure in PLHA in the post-cART era, for which urgent diagnosis was needed and was provided by liver biopsy. These patients had previously experienced cART in a developing

country. We conducted a literature review on DMAC disease to explore its epidemiology, risk factors, clinical manifestations, diagnosis, prognosis, treatment, and prophylaxis since the recognition of HIV/AIDS in 1981.

## Epidemiology

The first report of a DMAC case with HIV/AIDS occurred in 1982. A patient from Ohio (the United States), with a history of multiple candidiasis episodes in 1981, presented with a *Pneumocystis jirovecii* lung infection. The patient was readmitted a year later, with fever, splenomegaly, anemia, and lymphopenia<sup>1</sup>. At this time, an acquired immunodeficiency syndrome, later named HIV/AIDS, was still being recognized. Therefore, hematologic malignancy was suspected, and an exploratory laparotomy was performed, though there were no tumor findings. MAC was detected in multiple sites, including the bone marrow, liver, mesenteric lymph nodes, and blood<sup>1</sup>.

Within a few years, DMAC incidence had increased significantly and showed high mortality. MAC became one of the main pathogens affecting PLHA, alongside *Candida albicans*, *P. jirovecii*, and *Cytomegalovirus*<sup>5,12</sup>. Until 1987, in the United States, 5.5% of PLHA were diagnosed with disseminated NTM. Of these, 95% of infections were with MAC, and half of these infections were in inaugural AIDS patients<sup>3</sup>. MAC and HIV/AIDS incidence continued to increase in high-income countries until 1990. After this, diagnoses of DMAC more than doubled. The prevalence of DMAC reached 20% in PLHA in developed countries and 40% in patients with CD4 counts <10 cells/mm<sup>3</sup><sup>5,13,14</sup>. However, there were significant differences between developed and developing regions, as the prevalence of PLHA in African regions was 2.4-2.6%<sup>14</sup>. These differences may reflect different technologies used to establish DMAC diagnoses.

Overall, the epidemiological pattern of MAC incidence changed after the introduction of cART and prophylaxis: MAC incidence decreased significantly, even in patients with CD4 lymphocyte counts <50 cells/mm<sup>3</sup><sup>6</sup>. During the late cART period, MAC incidence dropped to 0.2 events per 1000 patient years<sup>7</sup>. Despite this decrease, the pooled frequency of MAC from 1992 to 2012 was 10.6%, while from 2000 to 2012, it varied between 3% and 10%, with higher rates in developing regions<sup>15</sup>. The initial proportion of NTM and MAC cases was maintained. More than half of NTM infections in PLHA are due to MAC infections with CD4 counts <50 cells/mm<sup>3</sup><sup>16</sup>.

**Table 1. Prophylaxis and treatment recommendations for disseminated *Mycobacterium avium* complex disease, according to the CDC, 2019**

Aim	Regimen	Recommendations
Primary prophylaxis	1. 1200 mg of azithromycin once weekly, or 600 mg twice weekly 2. 500 mg of clarithromycin twice daily	– Recommended only to those patients without cART use AND CD4 lymphocyte counts $<50$ cells/mm <sup>3</sup> – Discontinuing prophylaxis is recommended in patients under effective cART
Treatment	1. 500 mg of clarithromycin twice daily and 15 mg/kg of ethambutol daily 2. 500 mg of azithromycin daily, and 15 mg/kg of ethambutol daily	If a patient is not under cART, an additional drug may be needed. Options include: – 300 mg of rifabutin daily OR – 500 mg of levofloxacin daily OR – 15 mg/kg of amikacin daily

### Risk factors and prophylaxis

Risk factors for opportunistic diseases in HIV/AIDS include (1) immunological status, (2) ambient exposures, and (3) prophylaxis use. Before 1979, MAC disease risk factors were not well known, due to the disease rarity and to hematologic malignancies and immunosuppressive drugs that were correlated with the disease. Studies designed to understand the relationship between immunity and MAC found that MAC dissemination was strongly related to PLHA who had previously been diagnosed with other opportunistic infections, had high HIV viral loads, and had CD4 lymphocyte counts  $<25$ - $50$  cells/mm<sup>3,7</sup>. Thus, the introduction of cART directly influenced MAC epidemiology by improving immunological recovery<sup>6,7</sup>.

Ambient exposure to *Mycobacterium* spp. is an important factor in understanding infection development. Interestingly, MAC was first recognized as a *Bacilli* infection in chicken with disseminated granulomas and was, therefore, named avian tuberculosis. Soil may become a source of contamination due to bird feces, particularly if an individual has more than 5 years of cumulative occupational exposure<sup>17</sup>. In addition, disease dissemination can occur through water-related factors, including indoor pool use; consumption of spring water, raw seafood, or hard cheese; endoscopy; and showering outside the home<sup>18</sup>. In the past, screening for colonization did not have significant preventive effects, probably because in the cART era, colonized individuals who were taking antiretroviral therapy were not at significant risk for developing the disease<sup>19</sup>. Virulence factors from MAC may also play important roles in dissemination. One study found that MAC isolates from the pulmonary form of the disease had different virulence genes compared to isolates

from disseminated disease, but larger studies are needed to clarify this<sup>20</sup>.

The first approved chemoprophylactic drug against MAC was rifabutin, which was approved by the Federal Drug Administration in 1992-1993. Recommended dosing was 300 mg per day to PLHA, with CD4 lymphocyte counts  $<100$  cells/mm<sup>3,21</sup>. After rifabutin, macrolides were investigated, and a weekly 1200 mg dose of azithromycin demonstrated efficacy in reducing MAC disease incidence<sup>22</sup>. After cost-effectiveness studies, in 1997, the Centers for Disease Control (CDC) recommended azithromycin to patients with CD4 counts  $<75$  cells/mm<sup>3,23</sup>. During 2000-2005, discontinuing primary chemoprophylaxis was demonstrated to be safe in patients who had maintained CD4 counts  $>100$  cells/mm<sup>3</sup> for 3-6 months<sup>24</sup>.

Finally, in the late cART period, the incidence of MAC primary infections decreased independent of chemoprophylaxis usage, and the CDC recommended primary prophylaxis only to patients without immediate cART and with CD4 counts  $<50$  cells/mm<sup>3</sup>. They also recommended that prophylaxis be discontinued when patients initiated effective cART<sup>25</sup>. The recommendations regarding discontinuing secondary chemoprophylaxis have not changed for 2001; secondary chemoprophylaxis can only be discontinued in patients treated for at least 12 months, who have maintained CD4 counts  $>100$  cells/mm<sup>3</sup> for 6 months<sup>25</sup>. Summarized prophylaxis indications are shown in Table 1.

### Clinical manifestations and diagnosis

The MAC route of infection can occur through the respiratory or gastrointestinal tracts. MAC is an intracellular pathogen, and thus, after colonization, it infects local macrophages, which can control the infection,



cause local symptoms, or which can disseminate through the lymphatic system or blood<sup>26-29</sup>. In patients with HIV/AIDS, DMAC can be found in multiple organs, including the lungs, lymph nodes, liver, bowel, spleen, bone marrow, adrenal glands, urinary tract, brain, and blood.

DMAC usually presents with other opportunistic infections and common signs and symptoms of include weight loss, fever, night sweats, abdominal pain, diarrhea, lymphadenopathy, hepatosplenomegaly, or even hemophagocytic syndrome<sup>13,30</sup>. Anemia and elevated levels of alkaline phosphatase and lactate dehydrogenase are also related to DMAC disease<sup>30</sup>.

Depending directly from epidemiologic characteristics, a careful analysis must be done to differentiate between DMAC and disseminated tuberculosis. Regions with a high prevalence of *M. tuberculosis* may favor tuberculosis if peripheral lymphadenopathy, acid-fast *Bacilli* sputum, radiographic alterations, and a lack of AIDS-defining diseases are present. In contrast, patients living in regions with low rates of *M. tuberculosis*, who present with hepatosplenomegaly and elevated alkaline phosphatase and gamma-glutamyl transpeptidase levels, are more likely to have DMAC infections<sup>31</sup>.

During the late cART period, MAC infection may present as immune reconstitution inflammatory syndrome (IRIS). Once patients have basal CD4 lymphocytes counts <25-50 cells/mm<sup>3</sup> and high HIV viral loads, cART may efficiently control HIV viremia and flare up MAC symptoms as IRIS until 90 days after antiretrovirals<sup>32</sup>. Although MAC patients with IRIS are symptomatic for a longer period of time than MAC patients without IRIS, there is no difference in mortality rate between these groups<sup>32</sup>.

A diagnosis of MAC disease (local or disseminated) requires cultures and/or the demonstration of MAC in tissue. Cultures may come from the blood, bone marrow, urine, sputum, or stool samples. Two different culture techniques are used (1) lysis-centrifugation with posterior inoculation on liquid (i.e., liquid Middlebrook) or solid medium (i.e., Lowenstein-Jensen) or (2) automated systems with direct inoculation (i.e., MycoF/Lytic and BACTEC MGIT). Culture growth usually requires more than 10-15 days if a solid medium is used, or <10 days if a liquid medium is used. DMAC is usually diagnosed by blood or bone marrow cultures. Blood and bone marrow cultures do not differ significantly between sensitivity. Although both show a range of sensitivity between 30% and 100%, some studies argue that growth times are shorter in blood cultures<sup>10,33-36</sup>. In addition, it has been demonstrated that

accuracy is improved if combined culture techniques are used<sup>33</sup>.

Recently, newer techniques based on *Mycobacterium* spp. genetic analysis have been applied to MAC disease. Multigene sequencing allows a fast and highly accurate MAC diagnosis. In addition, multigene analyses may provide data on macrolides and aminoglycosides gene resistance, with high concordance to broth microdilution<sup>37</sup>. Another diagnosis option may be using multiplex PCR followed by dipstick chromatography<sup>38</sup>. In addition, whole-genome sequencing (WGS) has been applied to MAC disease<sup>39</sup>, where it is possible that it could have high accuracy in differentiating between *M. avium*, *Mycobacterium intracellulare*, and *Mycobacterium chimaera*. Diagnoses based on these new techniques will likely assist in gathering more accurate epidemiologic data. Low rates that were found in low- and middle-income countries previously may be due to a lack of technology for detecting this complex diagnosis. Moreover, different virulence characteristics among *M. avium*, *M. intracellulare*, and *M. chimaera* can also influence epidemiological scenarios<sup>40</sup>. Thus, DMAC should be assessed using WGS to clarify its overall genetic variability, genetic differences in relapses and prognosis, and to clarify its epidemiology in PLHA.

## Prognosis and treatment

There is a lack of information regarding the treatment and prognosis of DMAC infection in PLHA. Prognosis may directly depend on factors including the burden of mycobacteremia, antimycobacterial treatment, and the promptness of cART initiation. A high MAC burden in blood culture has been strongly correlated with death<sup>41</sup>. During 1980-1990, treatment was not well established for patients with positive MAC blood cultures. However, initial studies demonstrated improved survival rates in treated patients, even without guidelines regarding the appropriate antimycobacterial drugs (i.e., clofazimine)<sup>59,75,76</sup>. In support of this, the CDC recommends immediate cART initiation in patients with DMAC, as cART has been associated with a better prognosis<sup>25,41</sup>.

The majority of NTM infections in PLHA are due to MAC<sup>3</sup>. Overall, NTM infections in patients with low CD4 lymphocyte counts have been associated with death<sup>35</sup>. However, there are discrepancies in the literature, as immune differences between survivors and non-survivors are not significantly different in DMAC specific group<sup>41</sup>.

Initially, there were no recommendations for DMAC infections, and thus, there was a variety of drugs used in treatment. Multiple drug combinations were typically

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used, where first choices were clofazimine, ciprofloxacin, amikacin, rifabutin, and/or ethambutol<sup>42-44</sup>. Between 1995 and 2005, macrolides were gradually accepted as important options<sup>45-49</sup>. Survival rates were improved when clarithromycin and azithromycin were included in combination therapy<sup>48,49</sup>. Although the best combination therapy has not been well defined, macrolides have demonstrated efficacy even when used as a monotherapy<sup>47</sup>. The positive results of combining macrolides with ethambutol have been well established, and this course became the first-line treatment for MAC infection<sup>25,48,49</sup>. The addition of a third antimycobacterial drug (i.e., rifabutin) has shown variable results but may protect against macrolide resistance<sup>46,49</sup>. Current CDC treatment recommendations are (1) 500 mg of clarithromycin twice daily plus 15 mg/kg of ethambutol or (2) 500 mg of azithromycin plus 15 mg/kg of ethambutol daily, with an additional drug given to patients with high loads of mycobacteremia or who are not adherent to cART<sup>25</sup>.

## Conclusion

DMAC in PLHA in the post-cART period continues to occur, and differential diagnoses from the pre-cART period should be used depending on the immune status from the patient. Classical literature supports the idea of using blood and bone marrow cultures, although there is no established diagnostic process overall. Improved techniques (i.e. WGS and PCR) may provide options for diagnosis and may be able to utilize samples obtained from tissues other than blood and bone marrow. More studies are needed to clarify the accuracy of molecular diagnoses on DMAC. Finally, clinicians should be aware that the prognosis of DMAC is related to a prompt treatment regimen and that diagnosis is complex, particularly in developing countries.

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