Contents available at **PubMed**
www.aidsreviews.com

PERMANYER

AIDS Rev. 2020;22:9-15

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

João P. Marochi-Telles[1,2,3], Roberto Muniz Jr.[1,4], Jaques Sztajnbok[1,2], and Andre Cosme-de Oliveira[1,2]*

[1]Instituto de Infectologia Emilio Ribas; [2]Hospital de Clínicas da Faculdade de Medicina da Universidade de São Paulo; [3]AC Camargo Cancer Center; [4]Hospital Israelita Albert Einstein. São Paulo, Brazil

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^3. 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^3 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;22:9-15)**

Corresponding author: João Paulo Marochi Telles, jpmarochi@hotmail.com

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[1,2]. 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[3,4]. 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%[4,5]. Combination antiretroviral therapy (cART) changed this scenario, and a significant decrease in DMAC incidence occurred between pre-cART and post-cART periods[6,7]. At present, the incidence of DMAC infections in PLHA is two events per 1000 patient years[7].

Correspondence to:
*João Paulo Marochi-Telles
Av. Dr Arnaldo, 165 - 01246-900
São Paulo, Brazil
E-mail: jpmarochi@hotmail.com

Received in original form: 03-08-2019
Accepted in final form: 13-01-2020
DOI: 10.24875/AIDSRev.20000104

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[8-10], 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[11].

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^3). 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 normal. The CD4 cell count was 163 cells/mm^3, and the HIV viral load was 200,000 copies/mm^3. 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.

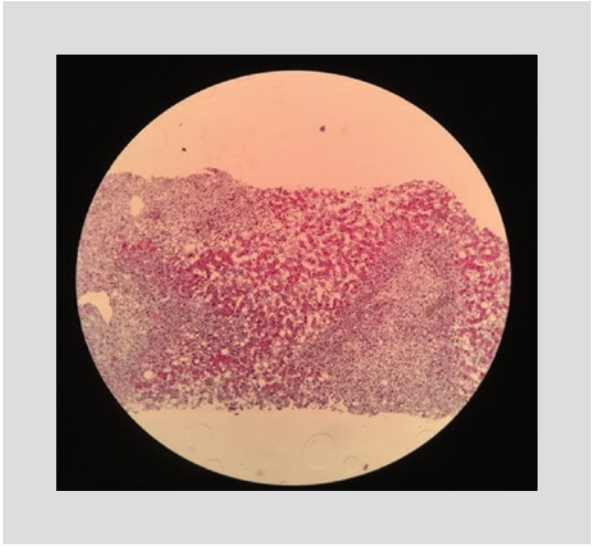

Figure 1. *Biopsy of granulomatous infiltrate in hepatic parenchyma.*

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^3), and thrombocytopenia (49,000 cells/mm^3) 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

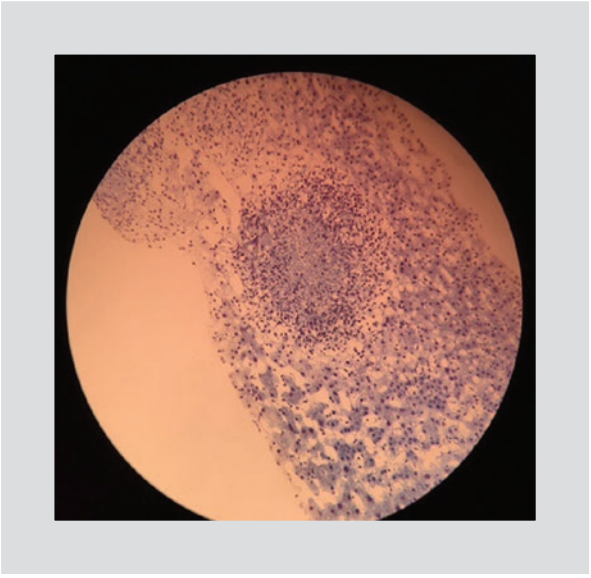

Figure 2. *Biopsy of granulomatous infiltrate in hepatic parenchyma.*

CD4 cell count was 61 cells/mm^3, and the HIV viral load was 300,000 copies/mm^3. 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[1]. 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[1].

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*[5,12]. 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[3]. 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^3.[5,13,14] However, there were significant differences between developed and developing regions, as the prevalence of PLHA in African regions was 2.4-2.6%[14]. 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^3.[6] During the late cART period, MAC incidence dropped to 0.2 events per 1000 patient years[7]. 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[15]. 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^3.[16]

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^3 – 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^3.[7] Thus, the introduction of cART directly influenced MAC epidemiology by improving immunological recovery[6,7].

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[17]. 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[18]. 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[19]. 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[20].

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^3.[21] After rifabutin, macrolides were investigated, and a weekly 1200 mg dose of azithromycin demonstrated efficacy in reducing MAC disease incidence[22]. After cost-effectiveness studies, in 1997, the Centers for Disease Control (CDC) recommended azithromycin to patients with CD4 counts <75 cells/mm^3.[23] During 2000-2005, discontinuing primary chemoprophylaxis was demonstrated to be safe in patients who had maintained CD4 counts >100 cells/mm^3 for 3-6 months[24].

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^3. They also recommended that prophylaxis be discontinued when patients initiated effective cART[25]. 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^3 for 6 months[25]. 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[26-29]. 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[13,30]. Anemia and elevated levels of alkaline phosphatase and lactate dehydrogenase are also related to DMAC disease[30].

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[31].

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^3 and high HIV viral loads, cART may efficiently control HIV viremia and flare up MAC symptoms as IRIS until 90 days after antiretrovirals[32]. 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[32].

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[10,33-36]. In addition, it has been demonstrated that accuracy is improved if combined culture techniques are used[33].

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[37]. Another diagnosis option may be using multiplex PCR followed by dipstick chromatography[38]. In addition, whole-genome sequencing (WGS) has been applied to MAC disease[39], 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[40]. 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[41]. 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). In support of this, the CDC recommends immediate cART initiation in patients with DMAC, as cART has been associated with a better prognosis[25,41].

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

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

used, where first choices were clofazimine, ciprofloxacin, amikacin, rifabutin, and/or ethambutol[42-44]. Between 1995 and 2005, macrolides were gradually accepted as important options[45-49]. Survival rates were improved when clarithromycin and azithromycin were included in combination therapy[48,49]. Although the best combination therapy has not been well defined, macrolides have demonstrated efficacy even when used as a monotherapy[47]. The positive results of combining macrolides with ethambutol have been well established, and this course became the first-line treatment for MAC infection[25,48,49]. The addition of a third antimycobacterial drug (i.e., rifabutin) has shown variable results but may protect against macrolide resistance[46,49]. 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[25].

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.

References

1. Centers for Disease Control (CDC). Pneumocystis carinii pneumonia among persons with hemophilia A. MMWR Morb Mortal Wkly Rep. 1982;31:365-7.
2. Centers for Disease Control (CDC). Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. Council of state and territorial epidemiologists; AIDS program, center for infectious diseases. MMWR Suppl. 1987;36:1S-15S.
3. Horsburgh CR Jr., Selik RM. The epidemiology of disseminated nontuberculous mycobacterial infection in the acquired immunodeficiency syndrome (AIDS). Am Rev Respir Dis. 1989;139:4-7.
4. Nightingale SD, Byrd LT, Southern PM, Jockusch JD, Cal SX, Wynne BA. Incidence of *Mycobacterium avium-intracellulare* complex bacteremia in human immunodeficiency virus-positive patients. J Infect Dis. 1992;165:1082-5.
5. Baril L, Jouan M, Agher R, Cambau E, Caumes E, Bricaire F, et al. Impact of highly active antiretroviral therapy on onset of *Mycobacterium avium* complex infection and cytomegalovirus disease in patients with AIDS. AIDS. 2000;14:2593-6.
6. Tumbarello M, Tacconelli E, de Donati KG, Bertagnolio S, Longo B, Ardito F, et al. Changes in incidence and risk factors of *Mycobacterium avium* complex infections in patients with AIDS in the era of new antiretroviral therapies. Eur J Clin Microbiol Infect Dis. 2001;20:498-501.
7. Collins LF, Clement ME, Stout JE. Incidence, long-term outcomes, and healthcare utilization of patients with human immunodeficiency virus/acquired immune deficiency syndrome and disseminated *Mycobacterium avium* Complex From 1992-2015. Open Forum Infect Dis. 2017;4:ofx120.
8. Mathuram AJ, Michael JS, Turaka VP, Jasmine S, Carey R, Ramya I. Mycobacterial blood culture as the only means of diagnosis of disseminated tuberculosis in advanced HIV infection. Trop Doct. 2018;48:100-2.
9. Munseri PJ, Talbot EA, Bakari M, Matee M, Teixeira JP, von Reyn CF. The bacteraemia of disseminated tuberculosis among HIV-infected patients with prolonged fever in Tanzania. Scand J Infect Dis. 2011;43:696-701.
10. MacGregor RR, Hafner R, Wu JW, Murphy RL, Perlman DC, Bermudez LE, et al. Clinical, microbiological, and immunological characteristics in HIV-infected subjects at risk for disseminated *Mycobacterium avium* complex disease: an AACTG study. AIDS Res Hum Retroviruses. 2005;21:689-95.
11. Rebollo MJ, San Juan Garrido R, Folgueira D, Palenque E, Díaz-Pedroche C, Lumbreras C, et al. Blood and urine samples as useful sources for the direct detection of tuberculosis by polymerase chain reaction. Diagn Microbiol Infect Dis. 2006;56:141-6.
12. Lerner CW, Tapper ML. Opportunistic infection complicating acquired immune deficiency syndrome. Clinical features of 25 cases. Medicine (Baltimore). 1984;63:155-64.
13. Havlik JA Jr., Horsburgh CR Jr., Metchock B, Williams PP, Fann SA, Thompson SE 3rd. Disseminated *Mycobacterium avium* complex infection: clinical identification and epidemiologic trends. J Infect Dis. 1992;165:577-80.
14. Fordham von Reyn C, Arbeit RD, Tosteson AN, Ristola MA, Barber TW, Waddell R, et al. The international epidemiology of disseminated *Mycobacterium avium* complex infection in AIDS. International MAC Study Group. AIDS. 1996;10:1025-32.
15. Heidary M, Nasiri MJ, Mirsaeidi M, Jazi FM, Khoshnood S, Drancourt M, et al. *Mycobacterium avium* complex infection in patients with human immunodeficiency virus: a systematic review and meta-analysis. J Cell Physiol. 2019;234:9994-10001.
16. Wang DM, Liao Y, Li QF, Zhu M, Wu GH, Xu YH, et al. Drug resistance and pathogenic spectrum of patients coinfected with nontuberculous mycobacteria and human-immunodeficiency virus in Chengdu, China. Chin Med J (Engl). 2019;132:1293-7.
17. Reed C, von Reyn CF, Chamblee S, Ellerbrock TV, Johnson JW, Marsh BJ, et al. Environmental risk factors for infection with *Mycobacterium avium* complex. Am J Epidemiol. 2006;164:32-40.
18. Horsburgh CR Jr., Chin DP, Yajko DM, Hopewell PC, Nassos PS, Elkin EP, et al. Environmental risk factors for acquisition of *Mycobacterium avium* complex in persons with human immunodeficiency virus infection. J Infect Dis. 1994;170:362-7.
19. Gadelha A, Accácio N, Grinzstejn B, Veloso V, da Silveira LB, Fandinho F, et al. Low incidence of colonization and no cases of disseminated *Mycobacterium avium* complex infection (DMAC) in Brazilian AIDS patients in the HAART era. Braz J Infect Dis. 2002;6:252-7.
20. Uchiya K, Takahashi H, Yagi T, Moriyama M, Inagaki T, Ichikawa K, et al. Comparative genome analysis of *Mycobacterium avium* revealed genetic diversity in strains that cause pulmonary and disseminated disease. PLoS One. 2013;8:e71831.
21. Nightingale SD, Cameron DW, Gordin FM, Sullam PM, Cohn DL, Chaisson RE, et al. Two controlled trials of rifabutin prophylaxis against *Mycobacterium avium* complex infection in AIDS. N Engl J Med. 1993;329:828-33.
22. Oldfield EC 3rd, Fessel WJ, Dunne MW, Dickinson G, Wallace MR, Byrne W, et al. Once weekly azithromycin therapy for prevention of *Mycobacterium avium* complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multicenter trial. Clin Infect Dis. 1998;26:611-9.
23. Freedberg KA, Cohen CJ, Barber TW. Prophylaxis for disseminated *Mycobacterium avium* complex (MAC) infection in patients with AIDS: a cost-effectiveness analysis. J Acquir Immune Defic Syndr Hum Retrovirol. 1997;15:275-82.
24. Brooks JT, Song R, Hanson DL, Wolfe M, Swerdlow DL, Adult and Adolescent Spectrum of Disease Working Group. Discontinuation of primary prophylaxis against *Mycobacterium avium* complex infection in HIV-infected persons receiving antiretroviral therapy: observations from a large national cohort in the United States, 1992-2002. Clin Infect Dis. 2005;41:549-53.
25. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available from: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.

26. Jacobson MA, Hopewell PC, Yajko DM, Hadley WK, Lazarus E, Mohanty PK, et al. Natural history of disseminated *Mycobacterium avium* complex infection in AIDS. J Infect Dis. 1991;164:994-8.
27. Hellyer TJ, Brown IN, Taylor MB, Allen BW, Easmon CS. Gastro-intestinal involvement in *Mycobacterium avium-intracellulare* infection of patients with HIV. J Infect. 1993;26:55-66.
28. Torriani FJ, Behling CA, McCutchan JA, Haubrich RH, Havlir DV. Disseminated *Mycobacterium avium* complex: correlation between blood and tissue burden. J Infect Dis. 1996;173:942-9.
29. Horsburgh CR Jr. The pathophysiology of disseminated *Mycobacterium avium* complex disease in AIDS. J Infect Dis. 1999;179 Suppl 3:S461-5.
30. Benson CA. Disease due to the *Mycobacterium avium* complex in patients with AIDS: epidemiology and clinical syndrome. Clin Infect Dis. 1994;18 Suppl 3:S218-22.
31. Hsieh SM, Hung CC, Chen MY, Hsueh PR, Chang SC, Luh KT. Clinical features and outcome in disseminated mycobacterial diseases in AIDS patients in Taiwan. AIDS. 1998;12:1301-7.
32. Smibert OC, Trubiano JA, Cross GB, Hoy JF. Short communication: *Mycobacterium avium* complex infection and immune reconstitution inflammatory syndrome remain a challenge in the era of effective antiretroviral therapy. AIDS Res Hum Retroviruses. 2017;33:1202-4.
33. Kilby JM, Marques MB, Jaye DL, Tabereaux PB, Reddy VB, Waites KB. The yield of bone marrow biopsy and culture compared with blood culture in the evaluation of HIV-infected patients for mycobacterial and fungal infections. Am J Med. 1998;104:123-8.
34. Dos Santos RP, Scheid K, Goldani LZ. Disseminated nontuberculous mycobacterial disease in patients with acquired immune deficiency syndrome in the South of Brazil. Trop Doct. 2010;40:211-3.
35. Kobayashi T, Nishijima T, Teruya K, Aoki T, Kikuchi Y, Oka S, et al. High mortality of disseminated non-tuberculous mycobacterial infection in HIV-infected patients in the antiretroviral therapy era. PLoS One. 2016;11:e0151682.
36. Hussong J, Peterson LR, Warren JR, Peterson LC. Detecting disseminated *Mycobacterium avium* complex infections in HIV-positive patients. The usefulness of bone marrow trephine biopsy specimens, aspirate cultures, and blood cultures. Am J Clin Pathol. 1998;110:806-9.
37. Huh HJ, Kim SY, Shim HJ, Kim DH, Yoo IY, Kang OK, et al. GenoType NTM-DR performance evaluation for identification of *Mycobacterium avium* complex and *Mycobacterium abscessus* and determination of clarithromycin and amikacin resistance. J Clin Microbiol. 2019;57:e00516-19.
38. Chikamatsu K, Aono A, Kawai A, Hata H, Iwamoto T, Igarashi Y, et al. Evaluation of Q gene mycobacteria: a novel and easy nucleic acid chromatography method for mycobacterial species identification. J Microbiol Methods. 2019;163:105657.
39. Operario DJ, Pholwat S, Koeppel AF, Prorock A, Bao Y, Sol-Church K, et al. *Mycobacterium avium* complex diversity within lung disease, as revealed by whole-genome sequencing. Am J Respir Crit Care Med. 2019;200:393-6.
40. Boyle DP, Zembower TR, Reddy S, Qi C. Comparison of clinical features, virulence, and relapse among *Mycobacterium avium* complex species. Am J Respir Crit Care Med. 2015;191:1310-7.
41. Horsburgh CR Jr., Metchock B, Gordon SM, Havlik JA Jr., McGowan JE Jr., Thompson SE 3rd. Predictors of survival in patients with AIDS and disseminated *Mycobacterium avium* complex disease. J Infect Dis. 1994;170:573-7.
42. Chiu J, Nussbaum J, Bozzette S, Tilles JG, Young LS, Leedom J, et al. Treatment of disseminated *Mycobacterium avium* complex infection in AIDS with amikacin, ethambutol, rifampin, and ciprofloxacin. California collaborative treatment group. Ann Intern Med. 1990;113:358-61.
43. Jacobson MA, Yajko D, Northfelt D, Charlebois E, Gary D, Brosgart C, et al. Randomized, placebo-controlled trial of rifampin, ethambutol, and ciprofloxacin for AIDS patients with disseminated *Mycobacterium avium* complex infection. J Infect Dis. 1993;168:112-9.
44. Parenti DM, Williams PL, Hafner R, Jacobs MR, Hojczyk P, Hooton TM, et al. A phase II/III trial of antimicrobial therapy with or without amikacin in the treatment of disseminated *Mycobacterium avium* infection in HIV-infected individuals. AIDS clinical trials group protocol 135 study team. AIDS. 1998;12:2439-46.
45. Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for *Mycobacterium avium* complex bacteremia in patients with human immunodeficiency virus infection. Veterans affairs HIV research consortium. Clin Infect Dis. 1998;27:1278-85.
46. Gordin FM, Sullam PM, Shafran SD, Cohn DL, Wynne B, Paxton L, et al. A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with *Mycobacterium avium* complex. Clin Infect Dis. 1999;28:1080-5.
47. Koletar SL, Berry AJ, Cynamon MH, Jacobson J, Currier JS, MacGregor RR, et al. Azithromycin as treatment for disseminated *Mycobacterium avium* complex in AIDS patients. Antimicrob Agents Chemother. 1999;43:2869-72.
48. Dunne M, Fessel J, Kumar P, Dickenson G, Keiser P, Boulos M, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated *Mycobacterium avium* infection in patients with human immunodeficiency virus. Clin Infect Dis. 2000;31:1245-52.
49. Benson CA, Williams PL, Currier JS, Holland F, Mahon LF, MacGregor RR, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated *Mycobacterium avium* complex disease in persons with acquired immunodeficiency syndrome. Clin Infect Dis. 2003;37:1234-43.