

# Disseminated nontuberculous mycobacteria infection in human immunodeficiency virus-infected patients

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Nontuberculous mycobacteria (NTM) infection can occur in both immunocompetent and immunocompromised patients, but disseminated NTM infection is mostly occurred in immunocompromised patients such as people using long-term immunosuppressants or patients with human immunodeficiency virus (HIV) infection, particularly in those with CD4+ T lymphocyte count <50 cells/mm<sup>3</sup>. Disseminated infection by NTM is considered a fatal acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection with high mortality in this population.

The incidence of disseminated *Mycobacterium avium* complex (MAC) disease is 20% to 40% in HIV-infected patients with advanced immunosuppression in the absence of effective antiretroviral treatment (ART) or chemoprophylaxis.<sup>[1]</sup> However, in the era of ART, researchers from the United States identified 37 disseminated nontuberculous mycobacteria (DNTM) cases among 7349 patients with a median annual incidence of 110/100,000 HIV person-years and the highest incidence in those with CD4+ T lymphocyte count <50 cells/mm<sup>3</sup> (5300/100,000 person-years) during 2007 to 2012.<sup>[2]</sup> The overall prevalence of any species of NTM in people living with HIV was 49% (96/196).<sup>[3]</sup>

Risk factors of susceptibility for DNTM infection are largely unknown. Existing research illustrates that natural immunity to mycobacteria relies on the interleukin 12 and interferon- $\gamma$  (IFN- $\gamma$ ) pathway, connecting myeloid cells (monocytes, macrophages, and dendritic cells) to lymphoid cells (T cells and natural killer cells).<sup>[4]</sup> Until now, at least seven autosomal mutations (in interleukin 12B, interleukin 12 receptor subunit beta 1, interferon-stimulated gene 15 [ISG15], interferon gamma receptor 1, interferon gamma receptor 2, signal transducer and activator of transcription

1, and interferon regulatory factor 8) and two X-linked mutations (in inhibitor of nuclear factor kappa B kinase regulatory subunit gamma and cytochrome B-245 beta chain), mostly presenting in childhood, have been reported to confer susceptibility to DNTM infection.<sup>[4]</sup> Genetic defects in any of these immune factors may lead to disseminated infection.

DNTM infection is considered an AIDS-defining condition, and the treatment involves optimization of immune function and prolonged use of combination of species-specific antimycobacterial drugs. Treatment is often complicated by the intrinsic or acquired drug resistance of NTM and adverse effects of the drug combinations, and treatment failure is common.<sup>[5]</sup>

Despite complex pathogenesis and difficult treatment, there is still considerable room for therapeutic improvement of DNTM. The treatment of AIDS with DNTM infection involves the combination of ART and long-term use of specific antibiotics. According to the updated Department of Health and Human Services guideline, ART should be started as soon as possible after the diagnosis of MAC disease, preferably at the same time that ART is initiated in patients with HIV and disseminated *Mycobacterium avium* complex (DMAC) disease who have not yet started effective ART.<sup>[6]</sup> A potentially large benefit of earlier ART initiation is to reduce the risk of AIDS-defining opportunistic infections and to improve the response to antimycobacterial therapy in the setting of advanced immunosuppression. As for patients who have been started ART, treatment should be continued. When drug interactions between antiretrovirals and antimicrobials are involved, the treatment regimen should be adjusted timely.<sup>[6]</sup> Unless ART leads to immune reconstitution,

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people living with HIV will require continuous antimycobacterial treatment.<sup>[6]</sup>

Auster *et al*<sup>[7]</sup> developed an innovative protocol that accelerates the growth kinetics of therapeutic assays in short-term *in vitro* quantitative assays. Their protocol demonstrated the capability to optimize the growth and characterization of *M. avium* and *M. intracellulare* independently and in combination for the systematic development of therapeutic drug testing. Sharma *et al*<sup>[8]</sup> designed a duplex polymerase chain reaction based on the sequence variation between the genes encoding catalase-peroxidase (KatG) of MAC and *Mycobacterium tuberculosis* (MTB). This method can facilitate quick differential diagnosis of DMAC and MTB infections in HIV patients. The rapid diagnosis is vital to inform urgent treatment decisions.

Bonfield *et al*<sup>[9]</sup> utilized *in vitro* and *in vivo* models of chronic NTM infection to evaluate the potential therapeutic use of human marrow-derived mesenchymal stem cells (hMSCs). Using these models, they identified donor-specific hMSCs potency against *M. avium* and *M. intracellulare*. The researches demonstrate that hMSCs are antimicrobial and anti-inflammatory *in vitro* and in the context of an *in vivo* sustained infection of either *M. avium* or *M. intracellulare* [Table 1]. Sharma *et al*<sup>[10]</sup> found that trehalose significantly reduced the HIV antibody and HIV antigen (HIV-p24) levels in *ex vivo*-infected peripheral blood mononuclear cells (PBMCs) or PBMCs from

treatment-naive HIV patients and also controlled mycobacterial survival within MTB-infected animals [Table 1].

A study showed the lymphocytes of patients with MAC-lung disease (MAC-LD) had attenuated function with regards to IFN- $\gamma$  production and increased apoptosis status, and this may be associated with an increase in the expression of the programmed cell death protein-1 (PD-1) pathway. By partially blocking PD-1 and its ligands, secretion of IFN- $\gamma$  increased from lymphocytes, and apoptosis status improved. Targeted regulation of the PD-1 pathway may have therapeutic potential for MAC-LD in the future, especially for patients who fail current medical treatment.<sup>[11]</sup> The effect of this novel therapeutic method in DNTM infection still needs to be identified.

Host-directed therapeutic (HDT) strategies offer several major advantages compared with conventional antibiotics: (a) HDTs can be effective against drug-resistant bacteria, drug-susceptible bacteria and potentially dormant mycobacteria; (b) HDTs are unlikely to result in bacterial drug resistance; (c) HDTs can synergize with antibiotics or shorten the duration of antibiotic treatment by targeting different pathways.<sup>[12]</sup> A review summarized the evidence supporting specific adjunctive, HDTs for MAC, with a focus on the repurposing of existing immune-modulatory agents targeting a variety of different cellular pathways.<sup>[13]</sup> The summarized HDT agents which are currently under investigation for MAC disease, as well as other HDTs and potentially targetable host pathways, were the mammalian

**Table 1: Recent advances in therapy of DNTM infection.**

Therapy	HDT agents/drugs	Advantage
hMSCs	hMSCs	hMSCs are antimicrobial and anti-inflammatory <sup>[9]</sup>
Trehalose	Trehalose	Activate autophagy and kill intracellular NTMs <sup>[10]</sup>
HDTs	Anti-PD-1/PD-L1 therapy Heme oxygenase inhibition IFN- $\gamma$ therapy Anti-TNF antibodies Non-steroidal anti-inflammatory drugs and corticosteroids Statins Metformin Clavanin-MO Thioridazine Heme oxygenase inhibition	(a) HDTs can be effective against drug-resistant bacteria, drug-susceptible bacteria and potentially dormant mycobacteria (b) HDTs are unlikely to result in bacterial drug resistance (c) HDTs can synergize with antibiotics or shorten the duration of antibiotic treatment by targeting different pathways <sup>[13]</sup>
New oxazolidinone	Linezolid, tedizolid	Against <i>M. abscessus</i> , with linezolid-like activity <i>in vitro</i> and <i>in vivo</i> <sup>[14]</sup>
Inhaled drugs	Inhaled NO and LAI	Reduced toxicity and improved efficacy <sup>[14]</sup>
Bedaquiline	Bedaquiline	Have clinical activity <sup>[14]</sup>
Clofazimine	Clofazimine	Synergistic with amikacin against <i>M. avium</i> and <i>M. abscessus</i> and it significantly prevented regrowth of NTM strains after clarithromycin and amikacin exposure <sup>[14]</sup>
$\beta$ -lactams in combination with $\beta$ -lactamase inhibitor avibactam	Avibactam	Against $\beta$ -lactamases in <i>M. abscessus</i> and <i>M. avium</i> <sup>[14]</sup>

DNTM: Disseminated NTM; HDTs: Host-directed therapies; hMSCs: Human marrow-derived mesenchymal stem cells; IFN- $\gamma$ : Interferon- $\gamma$ ; LAI: Liposomal amikacin for inhalation; NO: Nitric oxide; NTM: Nontuberculous mycobacteria; PD-1: Programmed cell death protein-1; PD-L1: Programmed cell death-ligand 1; TNF: Tumor necrosis factor.

target of rapamycin inhibitors, anti-PD-1/programmed cell death-ligand 1 therapy, heme oxygenase inhibition, IFN- $\gamma$  therapy, suppressing excessive tumor necrosis factor (TNF)- $\alpha$  activation (anti-TNF antibodies), broad suppression of inflammation (non-steroidal anti-inflammatory drugs and corticosteroids), targeting lipid metabolism and inducing autophagy (statins), activation of adenosine monophosphate-activated protein kinase and potentiation of macrophage effector function (metformin), immunomodulation and antimicrobial properties (clavanin-MO), and potentiation of macrophage effector function and antimicrobial activity (thioridazine).<sup>[13]</sup> HDTs against MAC represent a promising but underexplored avenue of research, which could hold great potential in improving microbiological and clinical outcomes [Table 1].

Additionally, several new drugs also show their effectiveness in treating nontuberculosis, such as oxazolidinone (linezolid and tedizolid), inhaled nitric oxide, and liposomal amikacin for inhalation, bedaquiline, clofazimine, and  $\beta$ -lactams in combination with  $\beta$ -lactamase inhibitor avibactam, such as avibactam.<sup>[14]</sup> Inhaled drugs could reduce toxicity and improve the efficacy of anti-DNTM. Clofazimine was synergistic with amikacin against *M. avium* and *Mycobacterium abscessus* and it significantly prevented the regrowth of nontuberculosis strains after exposure to clarithromycin and amikacin. Novel treatments are research priorities [Table 1]. Recently, a subunit vaccine ID91 (a recombinant fusion protein) combined with GLA-SE (glucopyranosyl lipid adjuvant, a toll like receptor 4 agonist formulated) indicated protection against *M. avium* in a mouse model.<sup>[15]</sup> Therefore, vaccines were worthy to be considered in this area.

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### Conflicts of interest

None.

### References

1. Nightingale SD, Byrd LT, Southern PM, Jockusch JD, Cal SX, Wynne BA. Incidence of *Mycobacterium avium*-intracellular complex bacteremia in human immunodeficiency virus-positive patients. *J Infect Dis* 1992;165:1082–1085. doi: 10.1093/infdis/165.6.1082.
2. Varley CD, Ku JH, Henkle E, Schafer SD, Winthrop KL. Disseminated nontuberculous mycobacteria in HIV-infected patients,

3. Lapinel NC, Jolley SE, Ali J, Welsh DA. Prevalence of nontuberculous mycobacteria in HIV-infected patients admitted to hospital with pneumonia. *Int J Tuberc Lung Dis* 2019;23:491–497. doi: 10.5588/ijtld.18.0336.
4. Wu UI, Holland SM. Host susceptibility to nontuberculous mycobacterial infections. *Lancet Infect Dis* 2015;15:968–980. doi: 10.1016/S1473-3099(15)00089-4.
5. Gil E, Sweeney N, Barrett V, Morris-Jones S, Miller RF, Johnston VJ, *et al.* Bedaquiline as treatment for disseminated nontuberculous mycobacteria infection in 2 patients co-infected with HIV. *Emerg Infect Dis* 2021;27:944–948. doi: 10.3201/eid2703.202359.
6. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H, *et al.* Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009;58:1–207. <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e324a1.htm/00053202.htm>.
7. Auster L, Sutton M, Gwin MC, Nitkin C, Bonfield TL. Optimization of in vitro *Mycobacterium avium* and *Mycobacterium tuberculosis* growth assays for therapeutic development. *Microorganisms* 2019;7:42. doi: 10.3390/microorganisms7020042.
8. Sharma S, Latawa R, Wanchu A, Verma I. Differential diagnosis of disseminated *Mycobacterium avium* and *Mycobacterium tuberculosis* infection in HIV patients using duplex PCR. *Future Microbiol* 2021;16:159–173. doi: 10.2217/fmb-2020-0091.
9. Bonfield TL, Sutton MT, Fletcher DR, Folz MA, Ragavapuram V, Somoza RA, *et al.* Donor-defined mesenchymal stem cell antimicrobial potency against nontuberculous mycobacterium. *Stem Cells Transl Med* 2021;10:1202–1216. doi: 10.1002/sctm.20-0521.
10. Sharma V, Makhdoomi M, Singh L, Kumar P, Khan N, Singh S, *et al.* Trehalose limits opportunistic mycobacterial survival during HIV co-infection by reversing HIV-mediated autophagy block. *Autophagy* 2021;17:476–495. doi: 10.1080/1548627.2020.1725374.
11. Shu CC, Wang JY, Wu MF, Wu CT, Lai HC, Lee LN, *et al.* Attenuation of lymphocyte immune responses during *Mycobacterium avium* complex-induced lung disease due to increasing expression of programmed death-1 on lymphocytes. *Sci Rep* 2017;7:42004. doi: 10.1038/srep42004.
12. Kiliç G, Saris A, Ottenhoff THM, Haks MC. Host-directed therapy to combat mycobacterial infections. *Immunol Rev* 301:62–83. doi: 10.1111/imr.12951.
13. Crilly NP, Aye SK, Karakousis PC. The new frontier of host-directed therapies for *Mycobacterium avium* complex. *Front Immunol* 2020;11:623119. doi: 10.3389/fimmu.2020.623119.
14. Wu ML, Aziz DB, Dartois V, Dick T. NTM drug discovery: status, gaps and the way forward. *Drug Discov Today* 2018;23:1502–1519. doi: 10.1016/j.drudis.2018.04.001.
15. Larsen SE, Reese VA, Pecor T, Berube BJ, Cooper SK, Brewer G, *et al.* Subunit vaccine protects against a clinical isolate of *Mycobacterium avium* in wild type and immunocompromised mouse models. *Sci Rep* 2021;11:9040. doi: 10.1038/s41598-021-88291-8.

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