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# Ionic liquids on the rescuing of conventional antimycobacterial drugs

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## EXTENDED-ABSTRACT

The incidence of infections by nontuberculous mycobacteria (NTM) is increasing worldwide, mainly those caused by Mycobacterium avium complex (MAC) species [1]. NTM are opportunistic pathogens that infect immunocompromised patients, namely those infected with HIV, with cancer or who were subject to a transplant. NTM are highly infectious and cause persistent infections due to their ability to easily form aerosols, to settle as biofilms and to resist to harsh environments, like chlorinated water [2]. In the host, mycobacteria proliferate inside phagocytic cells, such as macrophages. There, they multiply inside small vacuoles and control the intracellular vesicular trafficking inhibiting the phagosome-lysosome fusion, which allows them to escape the lysosomal acidic environment and to have access to nutrients [3]. NTM infections manifest primarily as pulmonary diseases, but can also affect other regions of the body, like the central nervous system, and cause lymphadenitis, which is the most common NTM-associated disease in immunocompetent children [4]. The treatment basis of slow-growing NTM, in which MAC is included, is a macrolide. Clarithromycin or azithromycin are the usual options. A regimen of monotherapy with macrolides is, however, very dangerous as it will often lead to drug resistance and consequent treatment failure. Thus, a three-drug macrolide-based regimen with ethambutol and a rifamycin, which usually lasts from 6 to 12 months, is the recommended treatment. The addition of a fourth drug to the regimen, like aminoglycosides or a fluoroquinolone, can be important in more severe cases and is essential in cases of macrolide-resistant MAC [5]. A very long multi-drug regimen like this, results in several issues to the patients, which decreases the probability of treatment success. It is thus urgent to find a new strategy to treat mycobacterial infections, including the repurposing of old drugs [6]. Ionic liquids (ILs) are organic salts made by the combination of two molecules with opposite polarities. Their remarkable physical and chemical properties contributed for their extensive use as green-solvents, improving the performance and safety of chemical procedures, as well as vehicles in sensors and drug delivery systems [7]. Recently, ILs have gained much attention in the area of drug development as antimicrobial agents, since they have shown improved solubility and bioavailability when compared to clinically approved drugs [8]. The right combination of cations and anions can provide innovative compounds that help combat resistance issues. The aim of our work is to evaluate the capacity of ILs based on conventional antimycobacterial drugs to inhibit the viability and growth of M. avium in axenic culture and inside bone marrow-derived macrophages (BMM). We are assessing if the activity and toxicity of these compounds are improved by being in the IL form instead of being administered individually or in combination. Our results show that ILs derived from each of two fluoroquinolones, ofloxacin or norfloxacin, and the antimycobacterial drug clofazimine cause a more significant decrease in the extracellular and intracellular mycobacterial viability than the fluoroquinolones administered individually. Moreover, the ILs are less toxic to the host cells than clofazimine. Another pair of ILs, which combine one classical antimalarial drug, chloroquine or primaquine, with the anti-tuberculosis drug aminosalicylic acid, also shows promising results: the ILs are more active against M. avium growing inside BMM than the three parental drugs

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by themselves. Therefore, our data encourage us to continue combining conventional anti-NTM antibiotics with molecules active against other pathogens in an IL form as a way to enhance their activity, improve pharmacological issues and combat resistances. In the future, we aim to test these ILs in more complex in vitro models of infection, such as biofilms and in vitro granulomas, taking advantage of fluorescent and bioluminescent reporter strains of M. avium, in order to better predict their clinical outcome and reduce the use of animals in preliminary drug testing.

**Keywords:** *Mycobacterium avium*, *In vitro* infection, Repurposing old drugs, Ionic liquids

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