# Statins cut tuberculosis treatment time in mice

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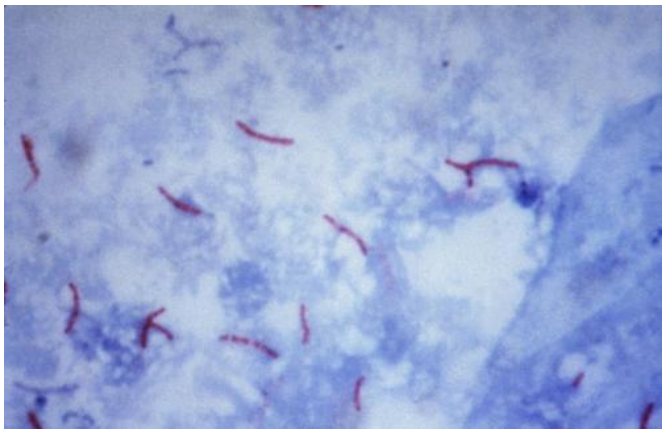

This photomicrograph reveals Mycobacterium tuberculosis bacteria using acid-fast Ziehl-Neelsen stain; Magnified 1000 X. The acid-fast stains depend on the ability of mycobacteria to retain dye when treated with mineral acid or an acid-alcohol solution such as the Ziehl-Neelsen, or the Kinyoun stains that are carbolfuchsin methods specific for M. tuberculosis. Credit: public domain

In a study using mice, the Johns Hopkins University School of Medicine infectious disease experts have added to evidence that statin drugs—known primarily for their cholesterol-lowering effects—can significantly reduce the time it takes to clear tuberculosis infection.

"If our results hold up in humans, the use of statins as adjuncts to standard drug treatment could confer substantial benefits to public health and the nearly nine million new TB patients diagnosed worldwide each year," says study author Petros Karakousis, M.D., associate professor of medicine in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine. "Because statins like the one we tested are already approved by the U.S. Food and Drug Administration and have a long history of safety in patients, the new data might substantially accelerate their repurposing for tuberculosis patients."

First-line treatment for tuberculosis, which consists of a combination of four antibiotics, should in theory cure all drug-susceptible infections if strict compliance can be assured. However, says Karakousis, a curative course of treatment usually requires six to nine months, with a minimum of 18 months for drug-resistant forms of the lung disease. To assure compliance, most patients in developed countries undergo directly observed therapy, in which a trained health care worker provides the prescribed drugs and watches patients swallow every dose—a strategy that mitigates spread of the disease but diverts resources from other needed medical care. In many developing countries, patients stop taking their antibiotics early when their symptoms abate, contributing to continued spread of tuberculosis in the community and the emerging problem of drug resistance.

Because new drugs that might shorten treatment duration are few in number and years from clinical use, Karakousis says his team's focus has been on repurposing already approved medicines that bolster the first-line regimen.

Toward that goal, the researchers focused on simvastatin, used by millions in the U.S. alone to reduce heart disease risk. In recent years, evidence has emerged that statins work, in part, by reducing inflammation by modulating the immune system, says Karakousis' colleague and study author Noton Dutta, Ph.D., research associate in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine.

In a report published just days before World TB Day by the *Journal of Antimicrobial Chemotherapy*, the Johns Hopkins team described its initial experiments with TB-infected cells growing in petri dishes. The researchers found that statins didn't directly kill the tuberculosis bacterium, but the addition of statin to infected cells helps stop

bacterial growth. The combination of statins and standard drugs cleared the tuberculosis bacteria more efficiently than cells receiving just the usual drugs.

Moving to infected mice, the researchers gave either the first-line regimen or those drugs plus simvastatin to animals six weeks after they were exposed to the tuberculosis bacteria in doses analogous to those standard for human patients. By counting the number of bacteria that remained in the animals' lungs over the course of treatment, the researchers found that adding the statin reduced the time to infection-free lungs from 4.5 months to 3.5 months.

Similarly, after 2.5 months, 3.5 months and 4.5 months of the standard treatment, mice had infection relapse rates of 100 percent, 50 percent and 0 percent. Adding simvastatin lowered the relapse rate to 50 percent after 2.5 months and to 20 percent after 3.5 months.

Together, says Karakousis, the results suggest that simvastatin could be an attractive candidate drug to reduce the amount of time patients with tuberculosis must be treated with the standard regimen, and he adds that preliminary data also suggest that other statins have similar effects. Consequently, he and his colleagues are currently studying other members of this class of drugs to identify the most effective statin for adjunctive therapy and the most effective dose.

Other important considerations in selecting the optimal statin, he adds, include cost and the potential for drug interactions with antiretroviral drugs used to treat HIV infection, which is common in patients with tuberculosis in many parts of the world.

The World Health Organization estimates that the cost of standard tuberculosis treatment is about $2,000 per patient in industrialized countries, but that amount rises more than a hundredfold for patients with drug-resistant strains of the disease. Statins vary widely in cost, with some generic versions costing as little as $4 per month through discount programs run by major chain stores to more than $600 per month for name-brand drugs not covered by insurance. In general, statins are well-tolerated by most patients. Severe side effects, such as liver or muscle damage, are extremely rare.

**More information:** Noton K. Dutta et al. Statin adjunctive therapy shortens the duration of TB treatment in mice, *Journal of Antimicrobial Chemotherapy* (2016). DOI: 10.1093/jac/dkw014

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