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TB treatment paradox: Mouse studies show body's own response helps TB bacteria survive

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Inhibiting a key immune response in mice during initial multi-drug treatment for tuberculosis could — paradoxically — shorten treatment time for the highly contagious lung infection according to new research from Johns Hopkins Children's Center and the Center for TB Research.

Shorter duration of drug therapy is key, researchers say, to increase treatment compliance for the growing global health threat posed by the disease.

In experiments described in the June 27 issue of *PLoS ONE*, the Johns Hopkins investigators compared a group of TB-infected mice receiving standard TB treatment of rifampin, isoniazid and pyrazinamide with another group that received standard TB treatment plus etanercept, a drug used to inhibit a protein known as tumor necrosis factor alpha, or TNF-α, to prevent immune responses.

TB infection causes an immune response that notoriously includes production of TNF-α, which is critical for the formation of TB granulomas — the hallmark tumors that form in the lungs and other parts of the body when the immune system tries to contain these bacteria. Paradoxically, this immune response is believed to wall off the bacteria, creating a sanctuary for "persistent" bacteria and, in turn, leading to the need for extended courses of treatment. Compliance with such treatment — daily doses of antibiotics for six months or more — is particularly

challenging in the developing world and has fueled an epidemic of multi-drug resistant TB, the researchers say.

"New and shorter TB treatments are needed to stop this scourge globally, but current treatments largely target actively replicating bacteria, rather than slow-replicating, persistent TB bacteria," says Sanjay Jain, M.D., an infectious disease specialist at Hopkins Children's Center and the senior author of this study.

Aware that TB patients taking TNF-α inhibitors to treat other conditions such as rheumatoid arthritis and Crohn's disease can "wake up" persistent TB bacteria, Jain and his team speculated that it might be possible to shorten TB treatments by using TNF-α inhibitors that keep microbes "awake" so that they could be "zapped" with standard TB treatments.

"We were surprised to find that this paradoxical approach actually works in mouse models of TB," Jain says.

During the initial six weeks of treatment, when TB bacteria were actively replicating, there was no significant difference in bacterial killing observed between the two groups of mice, Jain noted. But at weeks eight and 10, the group receiving standard TB treatment plus etanercept had a significantly lower bacterial burden than the group receiving just the standard TB treatment.

"This finding is important because it is during this later phase of infection and treatment, that TB bacteria multiply much more slowly, making up the so-called 'persisters' that lie 'asleep' and require protracted treatment," says Ciaran Skerry, Ph.D., the journal report's first author.

At 12 weeks, both groups had no bacteria visible on culture, but 27.8 percent of the group receiving standard TB treatment relapsed, while

only 10.5 percent of the ones treated with the standard treatment plus etanercept relapsed.

Jain says due to risks of reactivation disease with the use of TNF-α inhibitors, more studies for safety and efficacy need to be done in the laboratory before the treatment can be used in people.

Provided by Johns Hopkins University School of Medicine