

Doctor:  
MICHAEL WEIDEN

## Worst Case: TB + HIV

NYU researchers are hoping to understand how to treat one or both diseases without making the patient worse.

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▶ WHEN HIV JOINS FORCES WITH TB, THE results can be horrific. The neck bulges with lumps as big as an orange, filled with pus-like fluid teeming with the germs that cause TB. Occasionally, these bacteria travel through the blood and lymph vessels, forming lesions in the liver, spleen, and beyond. In chest X-rays, it looks as if the lung were studded with small nodules the size of millet seeds.

This gruesome scenario is rarely seen when TB is the lone affliction. But as HIV ravages the immune system, TB quickly and effortlessly spreads through the body. HIV's compounding effect on TB has long been known, but recently scientists have discovered that this pernicious partnership works both ways. TB, in turn, eases the path of HIV, dismantling the system that keeps the virus under control in the lungs, allowing it to mutate and multiply.

"If you have HIV and TB, then TB will kill you much more rapidly," notes Michael Weiden, M.D., associate professor of medicine and environmental medicine. In fact, TB is the leading cause of death among people who are HIV-positive, accounting for one-third of AIDS deaths worldwide.

Under normal circumstances, the lung is not a hospitable environment for HIV. An off switch of sorts keeps inflammation there to a minimum. Without this switch, even the smallest of irritants — dust, for example — would keep the lung chronically inflamed. Under these conditions, HIV is also held in check. The virus is limited to infecting perhaps one macrophage — a type of immune cell that serves as a reservoir for the virus — out of every 10 million.

But a bacterial infection such as TB changes all that. Attacked by the germs that cause TB, the lungs respond by recruiting neutrophils and T lymphocytes, which help the body fight pathogens. Neutrophils are deployed early and in great numbers to destroy any foreign invader. T cells are credited with being smarter, remembering previous offenders and releasing proteins that regulate the immune system.

Both types of cells shut down the off switch, allowing HIV to replicate. Other cell types also secrete proteins that speed up HIV's replication in macrophages and increase the rate at which HIV mutates, making it more virulent. As a result, HIV's presence in macrophages grows by as much as 100,000-fold.

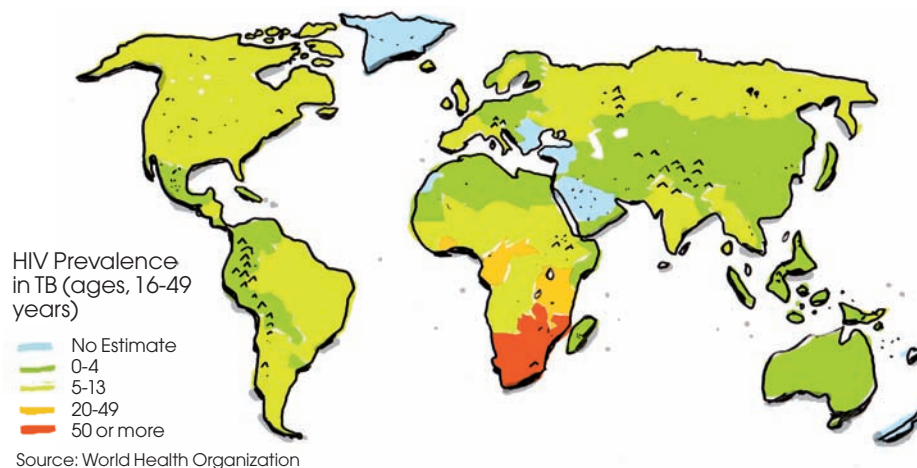
Dr. Weiden and his colleagues studied these interactions in 16 patients with HIV and TB. They reported in the May 2007 issue of the *Journal of Infectious Diseases* that TB infection activates neutrophils, and that these cells are responsible for driving the virus's replication, a surprising finding. Up to this point, HIV researchers had looked primarily at T lymphocytes, the virus's main host in the body. "Most

people focus on lymphocytes because they are the intelligent part of the immune system," says Dr. Weiden. "Macrophages do the dirty work, informed by lymphocytes. But here they can also be instructed by neutrophils."

Treating TB in conjunction with HIV is a lot more complicated than prescribing medicines for both. Each group of drugs can make the other less effective. When doctors know that a patient is infected with both diseases, they generally have to treat the TB first, employing HIV drugs only after the patient has improved. In about one in five cases, giving TB drugs first paradoxically makes the patient much worse, a phenomenon no one really understands yet. Often, because TB tests can't detect the bacterium in someone infected with HIV, doctors don't even realize that a patient has TB until it's too late.

Dr. Weiden and other researchers are now trying to tease out the molecular players involved in interactions between the deadly duo, in the hope that they can eventually understand how to treat one or both diseases without making the patient worse. ●

### Estimates of HIV Prevalence in New TB Cases, 2005



INFOGRAPHIC: PETER OUMASKI