Fighting the monster

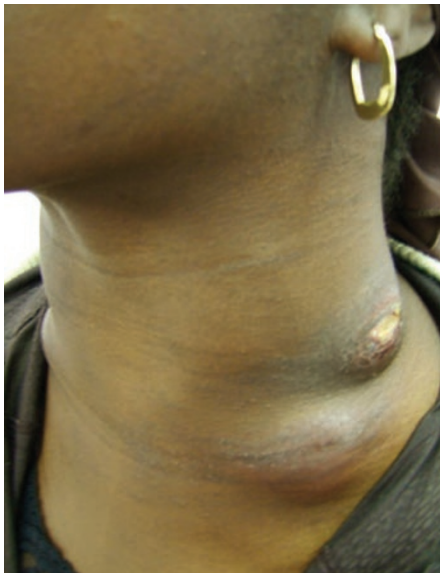
Co-infection with HIV and tuberculosis is a potent combination. **Amy Maxmen** investigates the impact of this deadly duo.

Sayoki Mfinanga calls it "the monster" for the way it wreaks havoc on a body.

Co-infection with HIV and tuberculosis (TB) can be devastating, triggering rapid weight loss, severe pneumonia and, often, a quick death.

Treating both diseases simultaneously does not improve matters, and in fact can cause fatal kidney and brain damage. "We don't understand what happens when you combine TB and AIDS drugs," says Mfinanga, director of the Muhimbili Medical Center at the National Institute for Medical Research in Dar es Salaam, Tanzania.

With weakened immunity, HIV-positive patients are highly susceptible to TB, and TB makes HIV disease progress quicker. According to a 2009 World Health Organization (WHO) report, there were more than 1.4 million cases of TB–HIV co-infection worldwide, resulting in about 0.5 million deaths in 2008. In sub-Saharan Africa, home to nearly 80% of those infected with both diseases, TB is the leading cause of death for HIV-infected individuals.



GRAEME MEINTJES

Many tuberculosis patients on the mend relapse after taking antiretroviral drugs, developing swollen neck glands and high fevers.

TB might be an important reason why HIV patients in the developing world suffer higher rates of mortality after beginning antiretroviral therapy, says Steve Lawn, associate professor of infectious diseases and HIV medicine at the Desmond Tutu HIV Centre in Cape Town. Although the probability of death after the first 12 months of antiretroviral therapy is about 1.8% in developed countries[1], Lawn and colleagues found that the rate is as high as 26% in sub-Saharan Africa[2].

"We consider co-morbidity of HIV and TB so prominent that it makes sense to use HIV money for TB research."

In May 2010, the Center for Global Health Policy drew together leaders in US science policy and advocacy to discuss the alarming increase in TB fuelled by HIV in the developing world. "In 2008, TB killed more people than anytime in recorded history," said Peter Cegielski, team leader for drug-resistant TB at the US Centers for Disease Control and Prevention. "In sub-Saharan Africa, that's purely because of HIV."

The deadly fallout of co-infection is forcing officials to take notice — and revise their priorities. "We consider co-morbidity of HIV and TB so prominent that it makes sense to use HIV money for TB research," says Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases. "In fact," Fauci says, "what I'm planning to do is to utilize some of our clinical trial networks that were only for HIV to study TB alone and TB with HIV."

Exacting its toll

In the past few years, access to HIV medicines in the developing world has improved. As more individuals have begun taking the drugs, however, they have faced unexpected complications. Interactions between drugs for HIV and TB can cause nausea, allergic reactions and joint pain. Rifampin, which is the mainstay of TB treatments, weakens the efficacy of antiretroviral drugs such as protease inhibitors and the non-nucleoside inhibitors efavirenz and nevirapine. The Bacillus Calmette-Guérin (BCG) TB vaccine can be lethal in HIV-infected infants.

Many TB patients who were previously improving with drugs relapse after starting a course of immune-boosting antiretroviral therapy, with a paradoxical reaction called immune reconstitution inflammatory syndrome (IRIS). "It may be that as antiretroviral drugs improve immunity, an inflammatory reaction is directed at the mycobacterium causing TB, and that reaction gives rise to the IRIS symptoms," says Graeme Meintjes, senior clinical researcher at the University of Cape Town.

IRIS typically occurs two weeks after TB patients begin taking antiretroviral drugs. The lymph nodes in the neck swell, high fevers hit and dry coughing begins. Some patients develop abscesses, stomach pain or kidney damage. About one person in every ten who develop IRIS has meningitis or inflammation of the brain, and many of these people die. Because definitions of IRIS vary and there are no diagnostic tests, reports of its frequency range from 8% to 43% of TB patients taking AIDS drugs[3].

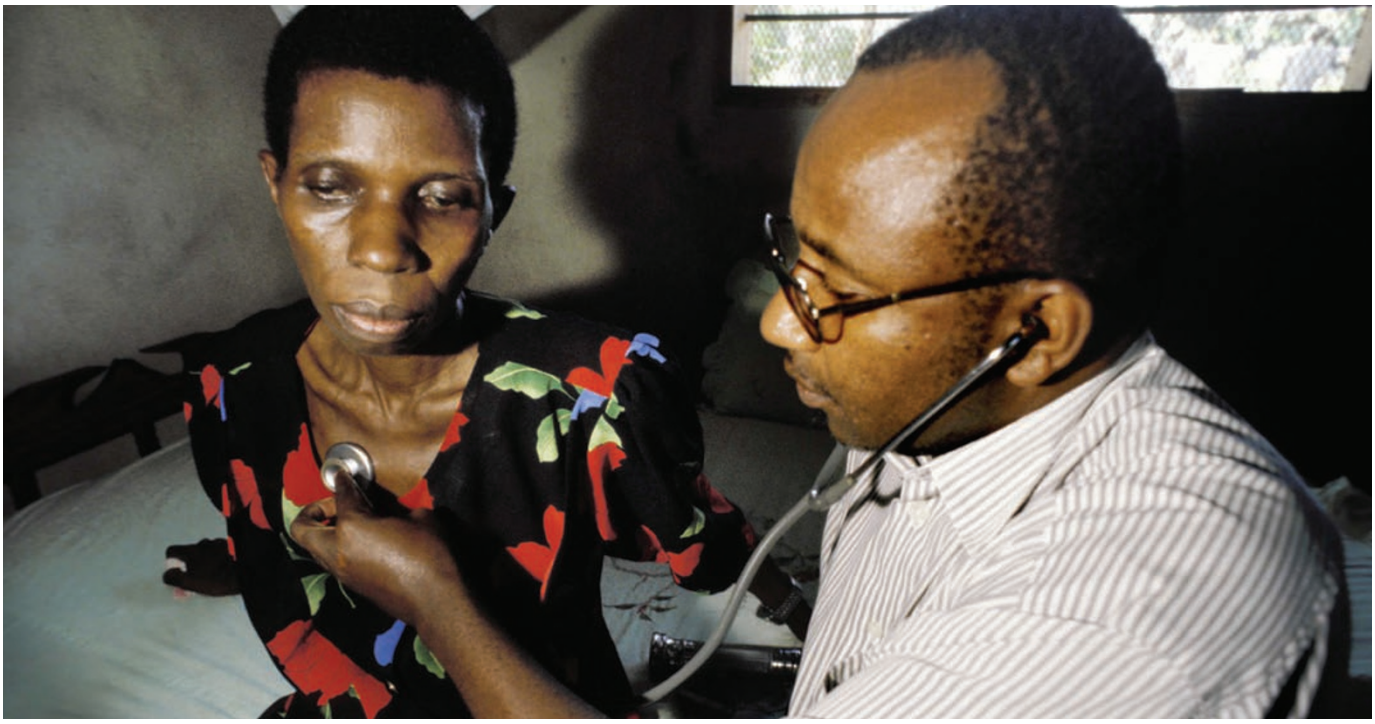
IRIS was first described in the mid-1990s, but has become more common since. "There's no question that the large-scale roll-out of antiretroviral therapy has helped millions of lives, but to be blind to the consequences of massive interventions, which are lifelong and delivered to a large proportion of your population, is not helpful," says Robert Wilkinson, professor of infectious diseases at the University of Cape Town.

In some cases, the immune-suppressing steroid prednisone can mitigate IRIS. Because of the risk of side effects such as diabetes, high blood pressure and osteoporosis, however, prednisone should not be given for more than a few months. Worse, if prednisone is given to people who have drug-resistant TB or another infection that could be mistaken for IRIS, it might exacerbate the condition.

Eye of the monster

One way to prevent IRIS might be in the timing of antiretroviral therapy. Some clinicians try to avoid IRIS by delaying antiretroviral drugs until after the patient has completed TB treatment, but a February 2010 report of a controlled clinical trial in South Africa cast doubt on this strategy. The researchers reported that twice as many people died in the group that delayed taking antiretrovirals as in the group that treated both diseases at the same time[4].

This has stirred some controversy: in June 2010, other researchers challenged the study



JORGEN SCHYTTE/STILL PICTURES

Co-infection with TB–HIV (as in the woman being examined, above) can be devastating, triggering rapid weight loss, severe pneumonia and, often, a quick death.

design[5], and questioned the influence of drug-resistant TB[6] and other factors that contribute to IRIS[7]. Three ongoing large trials are exploring the ideal time for those on TB treatment to begin antiretroviral therapy.

Other researchers are testing various combinations of antiretroviral and TB drugs. For instance, Wilkinson's team is assessing the safety of combining HIV treatments with the TB drug isoniazid. The WHO recommends isoniazid over rifampin for HIV-positive individuals in areas of high TB prevalence who do not show signs of TB, although it has not been rigorously tested in this setting.

Frustrated doctors say they hope that as each new HIV or TB drug enters the market, they will not need to scramble to learn how co-infected patients react.

"We quite often sit at meetings where pharmas try to convince us to use their [HIV] drugs for South Africa, but unless the drugs are compatible with pregnancy and TB, unless they are compatible with rifampin, they aren't very useful for us," says Linda-Gail Bekker, deputy director of the Desmond Tutu HIV Center. "They need to be tested in pregnant women and TB patients — but that rarely happens, and often that's an afterthought."

Some drug developers, however, are finally realizing the importance of developing TB solutions that work for HIV-positive patients. "You can't use a TB vaccine worldwide on a massive scale and screen everyone in advance for HIV — that's impractical," says Gordon Douglas, executive chairman of the Aeras Global TB Vaccine Foundation, a non-profit organization that partners with companies to develop TB vaccines.

The clinical trial for one of Aeras' lead candidates, AERAS-402, includes HIV-infected adults in South Africa. Animal data suggest that it will be safe for infants with HIV, Douglas says. Thus far, there have been no serious adverse reactions in adults. David McMurray, an immunologist at Texas A&M College of Medicine who is not affiliated with Aeras, says the vaccine "ought to be perfectly safe in HIV-positive individuals." Results are expected before 2013.

Clinical trials for HIV vaccines have not yet been designed with TB patients in mind, however. "A fundamental issue is that if someone has an episode of TB and develops immune dysfunction, will that affect the ability of that individual to mount a response when they're given an HIV vaccine?" asks Clive Gray, department head of HIV immunology at the National Institute for Communicable Diseases in Johannesburg. "The way to answer that is to do an HIV vaccine trial in people with immune memory to TB, but it's not really on the agenda now."

The spectre of drug resistance

Another looming threat is drug-resistant TB, particularly in crowded hospital wards where susceptible HIV-positive patients provide a reservoir for resistant strains. This became apparent in 2006 at a hospital in Tugela Ferry, South Africa, where 52 of 53 HIV-positive individuals infected with extensively drug-resistant TB died within a few months — many before they got the results from diagnostic tests.

Resistant strains of TB continue to sweep through HIV clinics. "We used to think that HIV was in Africa and [multidrug-resistant] TB was in Russia — well, not anymore," says Gail Cassell, vice president for scientific affairs at Eli Lilly in Indiana. "In 2008, we did big surveys in the Ukraine and in Latvia and found that HIV and [multidrug-resistant] TB rates are going up, and the two things show a very clear association."

Drug-resistant TB takes longer to treat and requires treatments that are 50 to 200 times more expensive. According to a 2010 WHO report, the estimated cost of treatment between now and 2015 will reach US$16.2 billion. Although new drugs to tackle resistant strains are being developed, it will take many years for them to be affordable for the majority. "In five years, there will not be new anti-TB drugs for use in developing countries because the compounds in the pipeline won't be ready until 2015 — if we're lucky," says Paul Nunn, coordinator of the WHO's Stop TB Partnership.

Perhaps answers will flow from recent investments by large organizations and institutes in rich countries. The Howard Hughes Medical Institute, for example, plans to invest US$60 million in its new research centre on TB–HIV in South Africa, slated to open by late 2012.

Those with fewer resources do what they can. Mfinanga's group is trying to determine the ideal timing for antiretroviral therapy in people infected with TB, knowing that it is small incremental advances in knowledge — and not a knight in shining armour — that will help slay the monster. ■

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CORRIGENDUM

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This Outlook article incorrectly stated that David McMurray is not affiliated with Aeras; in fact he is on the board of Aeras, but he is not directly working on the AERAS-402 vaccine.