

A clash of cultures

HIV and tuberculosis are a deadly combination, ravaging populations in Africa and Asia. But the two disease camps are too busy fighting each other to heed the crisis, says Apoorva Mandavilli.

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Photo: Louis Bellurget

When the wall came down, everything changed. People who had rarely agreed on anything met halfway, and together set a new paradigm for fighting two of the most devastating scourges the world has ever seen.

On the day they decided to break the wall, though, few realized its significance.

The wall had separated a tuberculosis (TB) clinic and an AIDS clinic in Khayelitsha, a poor township on the outskirts of Cape Town, South Africa. Khayelitsha is home to about a million people. It also has one of the highest burdens of HIV and TB in the world.

Every third pregnant woman in the township is HIV-positive, and the rate of new TB infections is 2,000 for every 100,000 people each year, nearly 20 times the global rate.

For years, Médecins Sans Frontières (MSF, or Doctors Without Borders) staff, who help run AIDS services in the township, had seen the same people lining up one day to receive TB drugs, the next for AIDS medicines, with separate folders and medical files in each clinic. The TB clinic had always been managed by the city and the newer AIDS services by the province.

Over the years, however, it has become increasingly obvious that the two diseases are inseparable and that their treatment too should be managed together. About 70% of

TB sufferers in Khayelitsha are HIV-positive, and TB is the leading cause of death in people with HIV.

One day in 2003, the MSF staff decided on impulse to tear down the wall and, with it, the arbitrary separation between the two diseases. "If we had asked permission first, it certainly wouldn't have been granted," says Eric Goemaere, head of MSF's South Africa mission.

"It seemed so obvious that we did it without thinking about it," Goemaere recalls. "It's only afterward when I saw how much resistance there was to doing it that I realized how symbolic it had been."

That same year, MSF took their solution one step further, opening an integrated clinic where those who present with TB are tested and treated for HIV and vice versa.

Outside Khayelitsha, however, relations between the HIV and TB communities remain less than cordial, undermining the fight against the crisis in Africa and elsewhere.

"HIV people think TB people are dull, out of date and they don't read published literature. TB people think HIV people can't see beyond individuals to the community," says Richard Chaisson, director of the Center for TB Research at Johns Hopkins University. "I work in both and I find it very frustrating."

Cross reactions

One in every three people is thought to be infected with the bacterium that causes TB, but few go on to ever show symptoms. In most parts of the world, TB is an old disease, dating back to the 1500s, and it wiped out the most susceptible people long before medicines became available.

But in Africa, TB has been present for little more than 100 years. "You just have less resistance to infection and disease in Africa," says Chaisson. "You add on the HIV epidemic, which obliterates resistance to the disease, and you have an epidemic."

In South Africa, Zimbabwe, Lesotho and Botswana, the incidence of TB has increased several-fold in the past decade.

When HIV and TB are present together, it's important that they are managed together because, at the simplest level, there are drug interactions to watch for. For example, the TB drug rifampin interferes with some non-nucleoside reverse transcriptase inhibitors and protease inhibitors, but not with the more expensive options.

In HIV-infected individuals, TB also progresses more quickly. By the time they turn up at the clinic, most are in dire need of medicines. The general practice is to start them

on TB therapy, which they usually need more urgently, and then give them antiretroviral drugs, which are increasingly available in Africa.

In theory, because AIDS drugs improve the cellular immune response, you would expect to see these people fight TB better and become healthier. And that's true in about 80% of cases.

The remaining 20% paradoxically get much worse, developing huge abscesses in the stomach and elsewhere, swollen lymph nodes and lesions in the brain. Many suffer horribly, shuttling in and out of hospitals for months. About one in seven dies.

"This is becoming very, very common all over Africa, it's being reported all over the place and in very significant numbers," says Robert Wilkinson, professor of infectious diseases at the University of Cape Town. "Nobody knows how to deal with it."

All in the timing

At a practical level, the debate has boiled down to timing: when should those with TB start

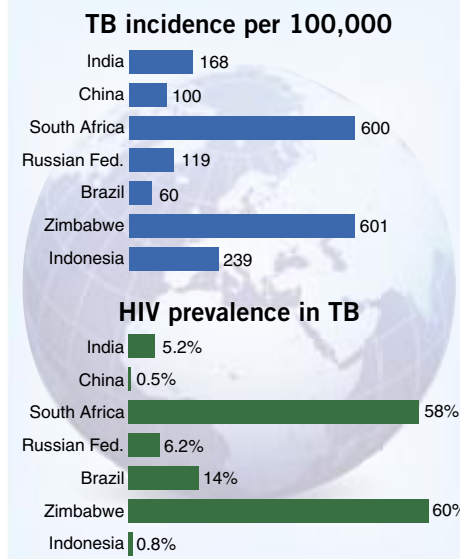
taking HIV drugs? Start too early, and they might develop this bizarre syndrome. Start too late, and they might die.

"If you were to ask five doctors what they would do, you'd get five different answers," says Salim Karim, director of Caprisa, a South African consortium of AIDS researchers. "This question is being answered in the developing world."

Scientists are just beginning to grapple with this syndrome, which they've dubbed IRIS for immune reconstitution inflammatory syndrome, but say it is devastating, both to those it afflicts and to the healthcare workers who treat them.

Some at the World Health Organization (WHO), however, are dismissive. "This is what you find when you talk to academic researchers whose job it is to go and look for problems," says Paul Nunn, coordinator of TB-HIV at the World Health Organization's Stop TB program. At a global scale, Nunn says, IRIS has not had a big impact, and has yet to be properly defined.

Nunn's comments are indicative of the



Deadly duo: The TB epidemic is at its worst wherever HIV is the most prevalent.

deep rift between basic researchers and the public health world. WHO officials rarely go to meetings where scientists present their findings,

Health agency pulls back on 'patronizing' approach to TB treatment

For more than a decade, the World Health Organization (WHO) has relied on Direct Observed Therapy Short-course, or DOTS, to fight tuberculosis (TB)—and for nearly as long, the strategy has been controversial.

The idea behind DOTS is that a healthcare worker should directly observe those infected swallow the TB drugs at least for the first two months of the six-month therapy. As the WHO likes to point out, the approach has successfully treated more than 22 million individuals worldwide. "In countries where they have done DOTS well, you don't see a high rate of drug resistance," says Chris Dye, coordinator of TB monitoring and evaluation for the WHO's Stop TB program.

Implementing DOTS well, however, is no easy task.

Activists and many on the ground have long argued that the DOTS approach is patronizing and impractical, and that it doesn't take individual circumstances into account. But in the past few years, it's become apparent to even the staunchest DOTS advocates that at least in Africa, the approach needs to be revised. "DOTS as a strategy has its limitations," says Dye.

For example, one TB clinic in Durban, South Africa, saw 9,000 infected individuals last year, nearly double compared with four years

earlier. The HIV epidemic has also complicated matters, partly because HIV-positive individuals are at greater risk of TB infection and because the DOTS-recommended diagnostic method for TB, the smear test, detects fewer than 40% of TB infections in HIV-infected individuals.

"DOTS will meet its goals everywhere but in Africa," says Richard Chaisson, director of the Johns Hopkins Center for TB Research. "If activities in Africa are ramped up substantially it might not, but based on current projections, it will fail."

The WHO's new global plan to stop TB, launched last year, is seen by many as a long-overdue concession to the reality on the ground, acknowledging that "addressing TB/HIV, multidrug resistant-TB and other challenges requires much greater action and input than DOTS implementation."

Apoorva Mandavilli, New York



WHO



Apoorva Mandavilli

Joining forces: The Médecins Sans Frontières clinic in Khayelitsha, South Africa, a rare example of collaboration between the TB and HIV communities, treating individuals like Pamela (above) for both diseases at the same time.

even though those results often inform policy decisions.

A decade ago, “the public health community was accused of being philistine or narrow-minded at best and alienated from the basic science community,” says Christopher Dye, Nunn’s colleague at the Stop TB program.

“There was some sense that we were enemies of each other and all this kind of nonsense—not anymore,” Dye says. “It’s way better than it was about ten years ago.”

Maybe so. But Nunn’s perspective is still far removed from the urgency with which most researchers on the ground speak of IRIS.

“The public health people who ignore the clinical importance of things, they undermine their credibility in the eyes of the people who run the program,” says Chaisson. “You need a public health approach, but you need to take care of patients.”

Power struggle

This disconnect is even more stark in the radically different cultures of the HIV and TB communities.

TB is an old disease and its approach, set primarily by the WHO, is faithful to the principles of classic public health: doing the best for the most people. With the perception that TB was curable, interest in TB research also dried up, and things are done much the same way they were decades ago.

“It’s extremely rigid from

case definition to therapeutic guidelines to standard operating procedures, it’s all written in stone and cast,” says Goemaere. “I’ve never seen so many guidelines. It’s almost Stalinian.”

The HIV community, in contrast, driven in part by activists, is focused on empowering the individual, with a heavy emphasis on applying the latest research.

The HIV-TB crisis has resulted in a power struggle between these two cultures, leading up all the way to the WHO’s own TB and HIV programs. “Everyone wonders who’s going to swallow

the other,” says Goemaere.

But there are small signs that things are changing, beginning with the WHO’s

admission that DOTS, the cornerstone of its TB programs, must take HIV into account (see box, page 269).

The WHO now recommends HIV testing for those infected with TB, preventive TB drugs for HIV-positive people and integration of TB and HIV programs.

In Rwanda and Kenya, 75% of TB sufferers are being tested for HIV, notes Nunn. “That’s up from nothing about a year and a half ago, that’s progress on an enormous scale,” he says. “We have illustrated that it can be done.” The WHO is meeting in March to expand the pilot scheme to more countries.

In South Africa, too, the integrated clinic in Khayelitsha is a resounding success, overflowing with those who are happy to get all their medicines in one place. The integrated programs may also help answer some fundamental questions about TB pathogenesis.

Researchers from the University of Cape Town are collecting samples from those who come to the clinics, studying HIV’s effect on TB progression and perhaps, by extension, what protects people from TB, says Wilkinson. “This is one of the greatest experiments in public health ever invented.”

Apoorva Mandavilli is Nature Medicine’s senior news editor.

Spotlight on... Mark Harrington

For a liberal arts graduate with no formal science background, Mark Harrington has a lot of influence on research for AIDS and tuberculosis (TB).

The head of the New York-based activist organization Treatment Action Group (TAG), Harrington commands respect from even the most senior AIDS and TB researchers. Last year, the group published a comprehensive analysis of funding for TB—showing, for example, that TB gets less than five percent of the amount spent on AIDS—that has quickly become a must-have resource in the community.

Harrington himself sits on the advisory boards of powerful agencies, including the US National Institutes of Health and the World Health Organization. With a four-year, \$4.7 million grant from the Bill & Melinda Gates Foundation, he is trying to strengthen support for TB by training AIDS activists on the issues, coordinating outreach with African activist groups, educating advocates and policy makers in Washington, DC, and pushing for more funds.

“We need to have strong activists in the countries most affected by HIV and TB so they can raise the awareness of the governments,” he says.

Harrington is no stranger to advocacy. In 1988, during the early days of the AIDS movement, he joined the famous ACT UP group in New York. He launched TAG four years later. Though still heavily involved in AIDS activism, Harrington in 2002 began campaigning for TB, a neglected disease with far fewer advocates.

“TB is a disease of the poor and the excluded and there’s never going to be a worldwide movement of TB activists the way there is with HIV,” says Harrington. “We’re not going to get to where we need to be without a massive investment into basic science.”

Alisa Opar, New York



Mark Harrington (left) with the WHO’s Haileyesus Getahun.