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HIV TB Co infection
Avoiding a Catastrophic Collision
Tuberculosis (TB) is the leading infectious killer of people with HIV/AIDS. In some countries of sub-Saharan Africa, more than 75 percent of patients with TB are HIV-positive (Global TB Control, WHO Report 2006) and 30 percent of people with HIV-associated TB disease experience mortality during treatment (Harries AD, et al, Lancet 2001; 357). Yet the standard regimen for treating TB relies on inadequate drugs that are 40 years old and interact adversely with some commonly prescribed antiretrovirals (ARVs). Side effects from TB drugs are also more common in people living with HIV, especially those on ARVs (Reid A, Lancet Infect Dis 2006; 6).

Although TB has been around for centuries, there has been little investment in new treatments since the 1960s when TB became less of a public health threat in the developed world. However, particularly in regions of the world with high rates of HIV/AIDS, the epidemic has been growing. People with latent tuberculosis who are HIV positive are at much higher risk of developing the active disease. Further, HIV causes recent TB infection to progress more rapidly (Reid, 2006).

Treatment of co-infection is lengthy and complicated. Currently, TB is treated with multiple drugs to effectively target what are thought to be different subpopulations of the TB bacterium and deter development of resistance. Four drugs (rifampin, ethambutol, isoniazid and pyrazinamide) are used in the treatment, which takes a minimum of six months. These drugs were first introduced between 1944 and 1965 and are now more than 40 years old. The current regimen is not effective against some drug-resistant forms of the disease and is incompatible with certain HIV/AIDS treatments.

Rifampin, a drug used in both the two-month “intensive” and four-month “continuation” phases of treatment, can cause drug reactions when combined with commonly-used HIV treatment regimens containing nevirapine or certain protease inhibitors. Rifampin induces an enzyme in the liver to metabolize some drugs, including certain AIDS medications, too quickly – reducing their potency and effectiveness.

In addition to these challenges, the WHO-recommended six month practice of direct observation, part of the Directly Observed Therapy Short-Course (DOTS) program, imposes significant demands on health care systems that suffer from lack of adequate human resources. Also, many people stop taking one or more of their medications when they feel better, potentially leading to the emergence of drug-resistant forms of TB. Recent evidence cited at the 2006 International AIDS Conference, also suggests very high rates of transmission of drug resistant forms of the disease in areas of the world with a high prevalence of HIV (International AIDS Conference, Toronto, 2006).

New Drugs Needed to Shorten and Simplify Treatment

Saving lives of TB/HIV co-infected patients will require new drugs. Because TB has primarily been a disease of poverty, until recently, there was little attention to improving therapy. In the late 1980s and early 1990s it became clear that the epidemic was on the rise and that drug resistance and TB/HIV were becoming significant problems. Realizing that the standard TB drugs were doing little to curb the epidemic, in 2000, key organizations in TB control, research and development met in Cape Town, South Africa to discuss concern over the lack of new drugs and established the Global Alliance for TB Drug Development (TB Alliance). The mission of the TB Alliance is to accelerate the development of a shorter, simpler regimen for the treatment of TB. It is important that new treatments are affordable, accessible, effective against drug-resistant strains and compatible with ARVs.

As a not-for-profit product development partnership, the TB Alliance leverages its capabilities in TB with the know-how and technologies of partners from the public, private and philanthropic sectors. Collaborators include pharmaceutical and biotechnology companies, academic laboratories, and multilateral institutions, advocates and service providers.
**Treatment of Latent TB infection**
The second strategy is widespread treatment of latent TB infection in high risk populations using isoniazid preventive therapy, or IPT, an inexpensive treatment that considerably reduces the risk of tuberculous progressing to active disease. Increased use of a nine-month course of IPT could prevent disease in the target population of HIV-infected individuals, as well as in those who are HIV-negative. As roughly one-third of the world’s population is infected with tuberculosis, IPT is one of the most promising methods of prevention.

**Combining antiretroviral and tuberculosis preventive treatment**
The third strategy involves combining antiretroviral and tuberculosis preventive treatment programs for reducing the risk of progressing from latent to active tuberculosis through prophylaxis and improving immune function through ART. ART lowers the risk of TB in people with HIV, but rates are still substantially higher than in HIV-uninfected individuals. Adding IPT to ART further reduces the likelihood of TB. But it is vastly underutilized.

These innovative yet straightforward techniques are currently being explored through large community-level studies in three countries. Thibela TB (“prevent” in Sotho) is a trial in South Africa to determine the impact of community-wide IPT on TB incidence and prevalence in gold miners, a population with a high rate of co-infection. The study will include >40,000 miners in 15 mine shafts. Each mine shaft and associated hostels, where the miners live, have been randomized to receive either community-wide IPT or targeting only high-risk individuals – miners with silicosis and/or HIV infection. In the mass IPT arm of the study, everyone in the mine, from executives to workers at the gold face, receives IPT after screening to rule out active TB. The expected reduction in TB incidence in the mines receiving massive IPT is 60 percent, or from 4,000 per 100,000 cases annually in the control mines to less than 1,600 per 100,000.

IPT is also the centerpiece of the second CREATE study in Brazil. THRío has been designed to determine whether routine detection and treatment of latent TB infection in the population served by HIV clinics in Rio de Janeiro reduces TB incidence.

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An example of this type of collaboration is a clinical testing program underway for the drug, moxifloxacin, that could reduce treatment time from six months to four months or less. Working together with Bayer Pharmaceuticals, the patent-holder for moxifloxacin, and clinical researchers from academic and public research institutes, the TB Alliance is coordinating human testing and data collection with the aim of approval for use against TB by regulatory authorities such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA).

The moxifloxacin program aims to replace one drug, but this substitution is just the start of shortening and simplifying treatment. In order to significantly improve TB therapy for HIV-infected and other patients, all four drugs in the current regimen may need to be replaced.

Given that attrition is inevitable in the drug development process, it is necessary to maintain a sufficiently large number of drug candidates to advance through development and replace the current outdated regimen. Over the last five years, the TB Alliance has developed a sizable number of potential drug compounds. This next generation of TB medicines is being tested for compatibility with ARVs and for TB patients co-infected with HIV/AIDS. A new moxifloxacin-containing regimen may be available as early as 2010 and an entirely new regimen excluding rifampin could be available within the next decade. Because most of these compounds have novel mechanisms of action, that is, they work against TB in new ways; they will also be effective against resistant strains of the disease.

**Delivering the Solution – Involving Communities**
Experience from HIV prevention trials has shown that the research and development process must engage communities of people who will eventually use the drugs. This includes both patients and managers of health programs. If a new drug is not designed to meet the needs of those who will eventually use it, and if no effort is made to promote adoption of new regimens, uptake will be slow and millions will die before the new drugs are available.

In earlier development stages, establishing the appropriate TB regimens for the settings in which they are used requires gathering data on the preferences of policy-makers, providers, advocates and patients on desired characteristics of potential new TB treatments. In the clinical phase, when drugs are tested in humans, the establishment of community advisory and consultation processes have become standard for AIDS drug and vaccine trials to ensure transparency, information exchange, and informed consent (Strauss RP, Am J Public Health, December 2001; 91(12)). Taking into account lessons learned from these models, the TB Alliance and partner organizations are currently working with stakeholders in countries such as Brazil, Tanzania, Uganda, South Africa and Zambia, where trials are planned, to develop culturally appropriate advisory structures.

To prepare for adoption and uptake once new drugs are available, the TB Alliance is organizing national TB program managers, standard-setting authorities, advocates, providers and patient groups, to develop plans for the introduction of new drugs at the country-level. These plans will include detailed steps and timelines for changing national regimen recommendations and essential drug lists and the “rollout” of new therapies.

**Financing Drug Development**
Advancing novel regimens depends on sufficient political will and financing. Over the next five years, the TB Alliance will need approximately $100 million, in addition to current support from donor foundations and governments to advance existing projects. Without this, it will not be possible to ensure development of new regimens. A number of commitments have been made recently that indicate increasing political support by key donor governments. At the June 2006 General Assembly high level meeting on AIDS (UNAIDS), the United Nations emphasized the need for accelerated scale-up of collaborative activities on tuberculosis and HIV in line with the Global Plan to Stop TB: 2006-2015 and investment in new drugs, diagnostics and vaccines appropriate for people with TB/HIV co-infection. This call, also voiced by the African Union in May, as well as by the G8 in St. Petersburg in July 2006, evidences political commitment from both donor and endemic countries.

Political statements and commitments, however, must translate into financial support. With sufficient funding from governments to bolster commitments by private foundations, such as the Bill & Melinda Gates and Rockefeller foundations, the ability to provide improved and shorter regimens that are safe and effective for TB/HIV-coinfected populations is within reach.

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For further information, contact: adeluca1@jesmail.johnshopkins.edu