

TB/HIV: An Orphan Disease?

Tuberculosis (TB) and human immunodeficiency virus (HIV) are tightly interwoven in a catastrophic, global syndemic. Worldwide, nearly 1.3 million patients with HIV develop TB each year, and 21% of the estimated 1.8 million HIV-associated deaths in 2009 were attributed to TB (1). Conversely, HIV has been responsible for a global resurgence of TB over the past two decades. It remains the single most important individual-level risk factor for progression from latent TB infection to active disease, and has greatly complicated programmatic control of TB—especially in resource-limited settings. In southern Africa, approximately 70% of newly diagnosed TB cases are co-infected with HIV. As a result, a recurrent theme in global public health research is the need to integrate TB and HIV research and health services (1). Despite the alarming incidence and severity of TB/HIV co-infection, it remains underfunded, understudied, and underrepresented at international research conferences.

This past year, at the 2010 Conference on Retroviruses and Opportunistic Infections, just 22 (2.2%) of the total 1,022 abstracts addressed TB/HIV co-infection (2). Only a single oral abstract session included TB/HIV presentations, and even this was a combined session including other opportunistic infections and metabolic complications of HIV. By contrast, 76 abstracts addressed Hepatitis C Virus—another important co-infection, but one that is responsible for a far lower global burden of disease and mortality than TB in HIV-infected individuals. This scarcity of TB/HIV research is, unfortunately, common at international Pulmonary and Infectious Diseases conferences. Only 8/1,435 (0.6%) and 37/5,500 (0.7%) posters, presentations, or symposia at the 2010 Infectious Diseases Society of America (IDSA) conference (3) and the 2010 American Thoracic Society conference (4), respectively, focused on TB/HIV co-infection. Although this may represent a low number of submissions, acceptances, or both, it is concerning, given the magnitude of the TB/HIV epidemic. While the International Union Against Tuberculosis and Lung Disease devotes a larger proportion of its annual conference program to TB/HIV co-infection, it has, to date, been primarily focused on programmatic and operational, rather than laboratory or translational, research (5). This under-representation of research on TB/HIV co-infection—reminiscent more of an orphan disease rather than one of the worst public health catastrophes of our time—may be due to the historic separation of TB and HIV research and care, underfunding of TB/HIV research, and the absence of a global market for TB drugs.

The separation of TB/HIV research between the medical specialties of infectious diseases and pulmonary medicine has historical roots. Pulmonary Medicine developed as a specialty in the pre-antibiotic era as a direct result of chest clinicians' experience in treating TB. Many of the important insights into pulmonary physiology and pathophysiology were the result of early studies in TB. Indeed, the American Thoracic Society was initially established in 1905 as the American Sanatorium Association (6). Early investigators of infectious diseases were

not active in TB, for it had already become the domain of pulmonary specialists, microbiologists, and public health doctors. These divisions have blurred somewhat over time, but while basic and translational research of HIV infection has been a focus of leaders in infectious diseases for almost three decades, there has been much less research focusing specifically on TB/HIV co-infection. To date, neither the field of infectious diseases nor that of pulmonary medicine has taken responsibility for promoting research on TB/HIV.

Historical divisions are only part of the problem. TB research remains underfunded by the National Institutes of Health (NIH) and private sector, relative to the global burden of disease. In 2009, the NIH spent \$169 million on TB research—a 19% increase compared with 2008, but a 10% decrease since 2007 (7). In contrast, the NIH has consistently spent approximately \$2.9 billion per year on HIV/AIDS since 2005. No matter how urgent the public health needs may be, therefore, researchers must follow available funding streams. Similarly, the absence of a Western market for successful TB therapeutics likely explains why the pharmaceutical and biotechnology industries have been embarrassingly slow to develop new drugs and diagnostics.

The lack of integration of TB and HIV research at scientific meetings has parallels in the programmatic management of both diseases. In the past several years, there have been increasingly urgent calls to integrate TB and HIV services, which have historically existed in isolation (8, 9). Despite the clinical and economic logic of such integration, however, implementation has been disappointingly limited. There are valid concerns about broad integration of HIV and TB services—notably, infection control in healthcare settings and combined medication toxicity—but these are manageable issues when properly anticipated (10). Although some progress in integration has been made, serious deficits remain. In 2008, provision of cotrimoxazole preventive therapy and antiretroviral therapy reached only one third of the levels targeted by the Global Plan for patients with TB/HIV co-infection (11). Implementation of the WHO “Three ‘I’s’” agenda (intensified case finding, isoniazid prophylaxis, and infection control) has also been far behind global targets (1).

Yet, there is evidence that the tide may at last be changing. Two key points appear to have seized the attention of the scientific community: (1) numerous antiretroviral treatment (ART) cohort studies showing high mortality rates in the first year after ART initiation—much of it attributable to TB (12); and (2) reports demonstrating dramatic and early mortality associated with drug-resistant TB in HIV-infected individuals (13). Each of these has been a stark reminder that TB control is essential to improving health in countries with high HIV-prevalence—even where access to ART is widespread. In response, the National Institute of Allergy and Infectious Diseases (NIAID) recently directed their HIV clinical trials networks to prioritize TB research (14). NIAID has also developed a task force to coordinate TB research across its divisions and has made new money available for this effort.

Innovative strategies by groups such as the TB Alliance and the Foundation for Innovative New Diagnostics (FIND) have sought to incentivize the creation of new therapeutic agents and

TB diagnostics. Areas of important recent investigation include near-patient, rapid diagnostic tests, novel genotypic analysis of *M. tuberculosis*, vaccine development, and the clinical testing of long-awaited new drugs. Although total NIH funding for TB did not increase in 2009 relative to 2007, several donors from the public and private sector (e.g., UK MRC, USAID, European Commission) increased their TB funding considerably. Still, total TB funding remains less than a third of projected needs, according to the Stop TB Partnership (7). Finally, the IDSA's Center for Global Health Policy has issued a brief to raise congressional awareness of the threat posed by "The Deadly Duo" (15).

Although these are all encouraging signs, much still needs to be done and it is critical that the momentum be maintained. As junior pulmonary and infectious diseases TB/HIV researchers, we call on our respective professional societies to follow through on the initiatives listed above and to promote an increased visibility of TB/HIV and TB research. Reasonable first steps might include a call for TB/HIV abstracts, creation of TB/HIV symposia within conference programs, and concerted advocacy for increased research funding from the public and private sectors. The scientific community should approach integration in the broadest sense—not just at the clinical and programmatic level, but also in clinical, translational, and bench research. The recent publication of both a *Clinical Infectious Diseases* supplement dedicated to TB and HIV (16) and a review of HIV-associated TB in *The Lancet* (17) is, hopefully, an indicator that these diseases will soon be routinely considered, treated, and studied together.

Over the past 30 years, research has produced deep understanding of HIV pathogenesis and more than 25 different medications, transforming the disease from a universal death sentence to a chronic, manageable infection. It is time that TB/HIV co-infection—still claiming so many lives worldwide and undermining the great strides of antiretroviral therapy—receives the due attention of our colleagues in the fields of infectious diseases and pulmonary medicine.

Author Disclosure: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors thank Gerald Friedland, Robert Horsburgh, and Philip Hopewell for their comments and input on drafts of this manuscript.

JAMES C. M. BRUST, M.D., M.S.
*Divisions of General Internal Medicine and
 Infectious Diseases
 Montefiore Medical Center and Albert Einstein
 College of Medicine
 Bronx, New York*
 and
*Tugela Ferry Care and Research Collaboration
 (TF CARES)
 Tugela Ferry, South Africa*
 MAX R. O'DONNELL, M.D., M.P.H.
*Division of Pulmonary Medicine
 Montefiore Medical Center and Albert Einstein
 College of Medicine
 Bronx, New York*
 and
*Centre for AIDS Programme of Research in
 South Africa (CAPRISA)
 Durban, South Africa*

JOHN Z. METCALFE, M.D., M.P.H.
*Francis Curry International Tuberculosis Center and
 Division of Pulmonary and Critical Care Medicine
 San Francisco General Hospital
 San Francisco, California*
 and
*Biomedical Research and Training Institute (BRTI)
 Harare, Zimbabwe*

References

1. World Health Organization. Global tuberculosis control 2010. Geneva: World Health Organization; 2010.
2. Programs and Abstracts from the 17th Conference on Retroviruses and Opportunistic Infections. Feb 16–19, 2010; San Francisco, CA. Available from: <http://www.retroconference.org>.
3. Programs and Abstracts from the 48th Annual Meeting of the Infectious Diseases Society of America. Oct 21–24, 2010; Vancouver, Canada.
4. Programs and Abstracts from the American Thoracic Society International Conference. May 14–19, 2010; New Orleans, LA. Available from: <https://cms.psav.com/cAbstract/itinerary/>
5. Programs and Abstracts from the 41st Union World Conference on Lung Health, Nov 11–15, 2010. Berlin, Germany. *Int J Tuberc Lung Dis* 2010;14:S1–S387.
6. Wilson JL. History of the American Thoracic Society: I. The American Sanatorium Association. *Am Rev Respir Dis* 1979;119:177–184.
7. Treatment Action Group. 2010 Report on Tuberculosis Research Funding Trends, 2005–2009; Nov. 2010.
8. Abdool Karim SS, Churchyard GJ, Abdool Karim Q, Lawn SD. HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response. *Lancet* 2009;374:921–933.
9. Corbett EL, Marston B, Churchyard GJ, De Cock KM. Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. *Lancet* 2006;367:926–937.
10. Howard AA, El-Sadr WM. Integration of tuberculosis and HIV services in sub-Saharan Africa: lessons learned. *Clin Infect Dis* 2010;50:S238–S244.
11. World Health Organization. Global tuberculosis control: key findings from the December 2009 WHO report. *Wkly Epidemiol Rec* 2010;85:69–80.
12. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS* 2008;22:1897–1908.
13. Gandhi NR, Shah NS, Andrews JR, Vella V, Moll AP, Scott M, Weissman D, Marra C, Lalloo UG, Friedland GH; Tugela Ferry Care and Research (TF CARES) Collaboration. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med* 2010;181:80–86.
14. Dieffenbach CW. Restructuring the HIV AIDS Clinical Trials Networks. Sept. 20, 2010 (accessed Jan 16, 2011). Available from: www.niaid.nih.gov/topics/HIV/AIDS/Documents/restructuringClinicalTrialsNetworks.pdf
15. Center for Global Health Policy. Deadly duo: the synergy between HIV/AIDS & tuberculosis. Arlington, VA: Infectious Diseases Society of America; 2010.
16. Mayer KH, Hamilton CD. Synergistic pandemics: confronting the global HIV and tuberculosis epidemics. *Clin Infect Dis* 2010;50:S67–S266.
17. Harries AD, Zachariah R, Corbett EL, Lawn SD, Santos-Filho ET, Chimzizi R, Maher D, Williams BG, De Cock KM. The HIV-associated tuberculosis epidemic—when will we act? *Lancet* 2010;375:1906–1919.

DOI: 10.1164/rccm.201010-1753ED