The Global Challenge of Tuberculosis among People Living with HIV

Overlapping Pandemics Require U.S. Government Leadership

AUTHORS
Phillip Nieburg
Sharon Stash
Alisha Kramer

A Report of the CSIS Global Health Policy Center

JUNE 2014

PART OF THE CSIS SERIES ON TUBERCULOSIS

CSIS | CENTER FOR STRATEGIC & INTERNATIONAL STUDIES

The Global Challenge of Tuberculosis among People Living with HIV

Overlapping Pandemics Require U.S. Government Leadership

Authors
Phillip Nieburg
Sharon Stash
Alisha Kramer

A Report of the CSIS Global Health Policy Center

June 2014

CSIS | CENTER FOR STRATEGIC & INTERNATIONAL STUDIES

About CSIS

For over 50 years, the Center for Strategic and International Studies (CSIS) has worked to develop solutions to the world's greatest policy challenges. Today, CSIS scholars are providing strategic insights and bipartisan policy solutions to help decisionmakers chart a course toward a better world.

CSIS is a nonprofit organization headquartered in Washington, D.C. The Center's 220 full-time staff and large network of affiliated scholars conduct research and analysis and develop policy initiatives that look into the future and anticipate change.

Founded at the height of the Cold War by David M. Abshire and Admiral Arleigh Burke, CSIS was dedicated to finding ways to sustain American prominence and prosperity as a force for good in the world. Since 1962, CSIS has become one of the world's preeminent international institutions focused on defense and security; regional stability; and transnational challenges ranging from energy and climate to global health and economic integration.

Former U.S. senator Sam Nunn has chaired the CSIS Board of Trustees since 1999. Former deputy secretary of defense John J. Hamre became the Center's president and chief executive officer in 2000.

CSIS does not take specific policy positions; accordingly, all views expressed herein should be understood to be solely those of the author(s).

Center for Strategic & International Studies
1616 Rhode Island Avenue, NW
Washington, DC 20036
202-887-0200 | www.csis.org

The Global Challenge of Tuberculosis among People Living with HIV

Overlapping Pandemics Require U.S. Government Leadership

Phillip Nieburg, Sharon Stash, and Alisha Kramer[1]

> "We will not realize the *AIDS-free Generation* goal if we do not address TB comprehensively."[2]
>
> "If not adequately addressed, TB has the potential to undermine the great strides that PEPFAR has made in rapidly expanding HIV care and treatment, and in decreasing TB/HIV-associated mortality…."[3]
>
> "Although preventable and curable, [TB] remains among the world's major killers of young adults, threatens HIV and antiretroviral rollout programs and saps strength and productivity from nations critical to improved global health and U.S. security."[4]

Human immunodeficiency virus (HIV) infection is widely acknowledged as one of the driving forces behind the global tuberculosis (TB) pandemic. Computer models estimate that about 1.1 million (13 percent) of the 8.6 million people newly identified with active TB disease in 2012 were people living with HIV (PLHIV). Twenty percent of TB patients who were actually tested for HIV in that year were found to be infected; 75 percent of these new coinfections[5] occurred in sub-Saharan Africa.[6] Of 1.3 million TB-related

---

[1] Phillip Nieburg, MD, is a senior associate with the CSIS Global Health Policy Center. Sharon Stash was previously the deputy director of the CSIS Global Health Policy Center and is currently a faculty affiliate with the Global Human Development Program, School of Foreign Service, Georgetown University. Alisha Kramer was previously a program manager with the CSIS Global Health Policy Center and is now a medical student at Emory University.

[2] Christine Lubinski, vice president for global health, Infectious Diseases Society of America, commentary during a CSIS Global TB Working Group meeting, September 10, 2013.

[3] PEPFAR, "Technical considerations provided by PEPFAR technical working groups for FY 2012 COPS [Country Operating Plans] and ROPS [Regional Operating Plans]," August 2011, 134, http://www.pepfar.gov/documents/organization/217761.pdf.

[4] U.S. TB expert Gerald Friedland, as cited in Rabita Aziz, "TB Budget Cuts Proposed as U.S. Plans Improved Global Disease Responses," *Science Speaks: HIV & TB News*, March 17, 2014, http://sciencespeaksblog.org/2014/03/17/global-tb-funding-cut-while-u-s-expands-global-health-security-agenda/.

[5] Coinfection terms such as "TB/HIV coinfection" are commonly used to describe the existence of active TB disease in people who are also people living with HIV (PLHIV). However, the term "coinfection" is not always technically precise when used in that context because the first phase of most human TB infections is usually a latent (inactive) phase in which the body is able initially to control the infection. Thus, most PLHIV who are also coinfected with TB still have a latent TB infection (and thus have an important opportunity to reduce their odds of developing active TB). Nevertheless, we will continue to use the

deaths reported in 2012, approximately 25 percent (320,000) were in PLHIV. Conversely, TB is the leading cause of severe illness and death in PLHIV, estimated to be responsible for at least 20 percent of all AIDS deaths globally. The initial scale-up of collaborative TB/HIV activities that saved 1.3 million lives from 2005 through 2011[7] needs to be expanded.

Introduction

In 1993, the first systematic autopsy study of African patients dying of AIDS found disseminated TB disease in 44 percent of them.[8] Struck by the frequent association of TB with AIDS deaths, the authors recommended that "prophylaxis or earlier diagnosis and treatment [of TB] in HIV-positive people should be the aim."

More than 20 years later, as TB infections in PLHIV have become a growing challenge,[9] particularly in sub-Saharan Africa, the world is still struggling to act on that program integration advice in a coordinated fashion.[10, 11]

HIV and TB disease each accelerates the progression of the other. In addition, TB disease in PLHIV is more difficult to diagnose and sometimes more difficult to treat, demanding a high degree of coordination between TB and HIV/AIDS control programs, and straining health systems' capacities. Successfully addressing the challenge of HIV-associated TB over the long term will require a reimagining of U.S. engagement in global TB control.

This paper lays out the key issues confronting the United States in its ongoing implementation of responses to TB among PLHIV and recommends ways for U.S. government policies and programs to better support the prevention and control of global TB/HIV coinfection.

"TB/HIV coinfection" term in some places in this paper because alternative terminology is sometimes awkward and because the term is still widely used—and understood—to describe TB disease in PLHIV.

[6] World Health Organization (WHO), *Global Tuberculosis Report 2013* (Geneva: WHO, 2013), Chapter 6: Addressing the Co-epidemics of TB and HIV, http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf?ua=1.

[7] WHO, *Global Tuberculosis Report 2012* (Geneva: WHO, 2012), 74, http://www.who.int/tb/publications/global_report/gtbr12_main.pdf.

[8] S. B. Lucas et al., "Contribution of Tuberculosis to Slim Disease in Africa," *British Medical Journal* 308 (June 11, 1994): 1531–33. The typical wasted presentation of African AIDS patients was at that time called "slim disease." A link between TB and HIV had been suspected since the 1980s but had not been well documented previously.

[9] The TB/HIV challenge is growing in part because one-third of PLHIV are thought to have latent TB infection (LTBI) and because HIV transmission is continuing. As PLHIV survive longer because of access to antiretroviral treatment, their numbers will increase.

[10] PEPFAR, "Technical Considerations Provided by PEPFAR Technical Working Groups for FY 2014 COPS [Country Operating Plans] and ROPS [Regional Operating Plans]," October 2013, 188, http://www.pepfar.gov/documents/organization/217761.pdf.

[11] Stop TB Partnership and WHO, *The Global Plan to Stop TB, 2011–2015* (Geneva: Stop TB partnership and WHO, 2011), 86, http://www.stoptb.org/assets/documents/global/plan/TB_GlobalPlanToStopTB2011-2015.pdf.

Biology and Epidemiology of TB Infection among PLHIV

At least one-third of the world's population is estimated to have a latent infection with *Mycobacterium tuberculosis*, the bacterium that causes TB. In some countries, the proportion of latent TB-infected individuals is far higher. Fortunately, the great majority of these TB infections continue to remain latent, as the body's immune system successfully contains the initial TB infection. People with a latent TB infection (LTBI) pose little threat to others, since LTBIs are not contagious.

The prognosis of LTBI is very different, however, among the nearly 40 million PLHIV. Because HIV infection suppresses the immune system, coinfection with HIV increases the risk of progression from LTBI to active TB by up to 50 times.[12] In fact, HIV infection is the strongest known risk factor for the progression of LTBI to active TB disease. Whereas people with LTBI who are *not* also infected with HIV face about a 10 percent chance of developing TB disease *over their lifetimes*, about 10 percent of PLHIV develop TB disease *every year* in the absence of antiretroviral therapy.

Why Should the United States Be Concerned about TB among PLHIV?

Put simply, the TB and HIV pandemics form a deadly synergy in many countries. The underlying biology of these diseases predicts that PLHIV with active TB disease are far more likely to die than are other PLHIV. In addition, preventing the development of TB disease in PLHIV can help reduce overall TB transmission in households and communities.

TB remains the leading infectious killer of PLHIV. Although the conventional wisdom is that about one-fifth of all AIDS deaths are due to TB, that proportion may be a significant underestimate. In fact, a recent review of autopsy studies among AIDS patients found generally higher rates of widespread TB disease.[13] TB was considered to be the specific cause of death in 32–45 percent of fatal AIDS cases; some of these TB infections had not been diagnosed before death.

Suppression of the host immune system in PLHIV can also make diagnosis of TB more difficult.[14] Improving the capacity of national health systems to screen all PLHIV for active TB disease and to treat PLHIV found to have active TB will require investments in new and more sensitive diagnostic testing technologies as well as a further strengthening of the overall capacities of national TB and HIV/AIDS programs to provide necessary access to screening, diagnosis, and treatment.

---

[12] WHO, "Frequently Asked Questions about TB and HIV," http://who.int./tb/challenges/hiv/faq/en/.
[13] Janneke A. Cox et al., "Autopsy Causes of Death in HIV-Positive Individuals in Sub-Saharan Africa and Correlation with Clinical Diagnoses," *AIDS Review* 12, (2010): 183–94; and Diane V. Havlir, "State of the HIV/TB Epidemic: Opportunities and Challenges" (paper presented at the 18th Core Group Meeting of the TB/HIV Working Group, Maputo, Mozambique, April 12, 2013), http://www.who.int/tb/challenges/hiv/havlir_state_of_the_epidemic.pdf?ua=1.
[14] Because of immune system changes in PLHIV, commonly used TB screening tests such as skin tests and chest X-rays are less sensitive for diagnosing TB disease in that group.

Protecting the Beneficiaries and Legacy of the President's Emergency Plan for AIDS Relief

A recent summary from the Technical Working Group of the President's Emergency Plan for AIDS Relief (PEPFAR) emphasized the serious concern felt in some quarters that TB among PLHIV could undermine PEPFAR's striking HIV treatment success.[15] It seems clear that responsibly protecting the life-saving benefits of HIV/AIDS care, including the more than $50 billion U.S. resource investment in PEPFAR,[16] will require ongoing, focused attention on the prevention of future TB disease and death among PLHIV.

In fact, a strong disease-prevention approach to TB among PLHIV is needed to realize the full benefits of otherwise effective antiretroviral treatment (ART). This approach can take several forms: first, ART prevents one-half to two-thirds of the short-term risk that PLHIV will develop TB disease.[17] Expanded use of ART has led to a striking decrease in AIDS-related deaths worldwide but further expansion is needed.

Second, beyond ART use, routinely screening PLHIV for TB disease—as is recommended by WHO for every clinical encounter—can lead to early and effective TB treatment of PLHIV found to have TB disease. Moreover, most of the PLHIV found to not have active TB disease can begin to receive effective therapy to *prevent* the eventual development of TB disease.

Finally, implementing measures to prevent TB transmission in clinics and other health facilities that serve PLHIV can reduce the risk of TB disease among both that group and, equally important, among the frontline health workers who serve in those facilities, a group that has been shown to have an increased risk of developing TB disease. Again, ensuring the success of each of these measures is likely to require a strengthening of national and local TB programs.

The "Three I's" Approach to Addressing TB in PLHIV

As noted in the current Lantos-Hyde U.S. TB strategy,[18] U.S. agencies are aware of the urgent need to reduce the prevalence of TB in communities highly affected by HIV. Experts agree that the only three ways to reduce the number of active TB infections in a community are: (1) reducing TB transmission; (2) reducing reactivation of latent TB infection; and (3) reducing HIV transmission.[19] For people already infected with HIV, prevention of TB infection and disease can be enhanced by preventing exposure to other people with TB disease and/or by decreasing the odds that an initial LTBI can

[15] PEPFAR, "Technical considerations provided by PEPFAR technical working groups for FY 2014 COPS [Country Operating Plans] and ROPS [Regional Operating Plans]," October 2013, 188.
[16] PEPFAR, "Shared Responsibility-Strengthening Results for an AIDS-free Generation: Latest PEPFAR Funding," March 2014, http://www.pepfar.gov/documents/organization/189671.pdf.
[17] UNAIDS, *Global Report: UNAIDS Report on the Global AIDS Epidemic 2013* (Geneva: UNAIDS, 2013), Chapter 5: Halve tuberculosis deaths among people living with HIV by 2015, http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf.
[18] USAID, "Lantos-Hyde United States Government Tuberculosis Strategy," March 24, 2010, http://pdf.usaid.gov/pdf_docs/PDACP707.pdf.
[19] Peter Godfrey-Faussett and Helen Ayles, "Can we control tuberculosis in high HIV prevalence settings?" *Tuberculosis* 38, (2003): 68–76.

progress to TB disease. These goals can be reached through various combinations of infection control activities, use of isoniazid preventive therapy, and early and intensive ART use.

With these realities in mind, the U.S. government's current strategy to address the prevention aspects of TB in PLHIV is built around the "Three I's" approach (Box 1), promulgated by WHO and the Stop TB Partnership,[20] which aims to reduce the burden of TB among PLHIV.[21]

Box 1: The "Three I's" to Address TB among PLHIV

- *Intensified Case Finding:* Ensure screening for TB disease among PLHIV at every clinical encounter; ensure needed referral to confirm or rule out TB diagnosis.
- *Isoniazid Preventive Therapy (IPT):* Provide IPT for PLHIV without current TB disease.
- *Infection Control for Tuberculosis:* Implement effective TB infection control policies to reduce spread of TB in locations where PLHIV are likely to congregate.

1. *Intensive Screening for HIV-associated TB among PLHIV*. PLHIV should be screened for symptoms of TB disease at every clinic or hospital visit,[22] using a simple four-question WHO symptom-screening tool that asks about a history of current cough, fever, weight loss and "night sweats."[23] Any PLHIV who reports one or more of these symptoms should be referred for a thorough evaluation for TB and other diseases.[24]

2. *Isoniazid Preventive Therapy (IPT).* PLHIV without any of the symptoms of TB disease should be offered TB preventive therapy with isoniazid, an inexpensive and widely available drug. In people with LTBI who are *not* infected by HIV, six months of TB preventive therapy with isoniazid significantly reduces the lifetime risk that their latent TB will progress to active TB disease.[25] In PLHIV with LTBI and a positive TB skin test, the effect of isoniazid preventive therapy (IPT) is slightly smaller than its effect in people not infected with HIV but still significant. In settings with intense transmission of *M. tuberculosis*, once IPT has been stopped, the preventive effect appears to wane over time. In such settings with high and ongoing risk to PLHIV of *new* TB infections, the optimal duration of IPT among

[20] USAID, "Lantos-Hyde United States Government Tuberculosis Strategy," 14.
[21] See WHO, "Scaling up the Three I's for TB/HIV," http://www.who.int/hiv/topics/tb/3is/en.
[22] PEPFAR, "Technical considerations provided by PEPFAR technical working groups for FY 2014 COPS and ROPS," October 2013, 190.
[23] WHO, *WHO policy on collaborative TB/HIV activities: Guidelines for national programmes and other stakeholders* (Geneva: WHO, 2012), http://whqlibdoc.who.int/publications/2012/9789241503006_eng.pdf?ua=1.
[24] When available, the Xpert MTB/RIF assay or similar enhanced test should be used as the initial diagnostic test for PLHIV with possible TB.
[25] Successful *treatment* of active TB disease requires at least four different drugs. Because isoniazid alone cannot cure TB disease, active TB disease must be ruled out before giving patients isoniazid alone.

PLHIV has yet to be resolved, but, as is now the practice with ART, lifelong IPT may ultimately be necessary.[26]

Parenthetically, although ART use reduces the risk that PLHIV will develop TB, taking ART does not totally eliminate that TB mortality risk. In fact, recent South African data indicate that, even when taking long-term ART, PLHIV have TB mortality risks more than four times that of people not infected with HIV.[27] Use of IPT by PLHIV taking ART results in a still further reduction of their TB risk.[28]

3. *Infection Control to Prevent Transmission of Tuberculosis.* Clinics and hospitals that treat PLHIV or test and counsel for HIV are also places where people with undiagnosed active TB are likely to congregate. Developing and implementing effective infection control policies and practices in such places is critical to help limit the spread of potentially lethal TB infections among PLHIV. The U.S. Agency for International Development (USAID) and the Centers for Disease Control and Prevention (CDC) have collaborated in the development of such programs.

Beyond the original "Three I's," two additional "I" priorities have been suggested[29]: *Integrated approach to TB/HIV* and *Intensified treatment with ART*.

4. An *Integrated TB/HIV approach* refers to the integration of TB screening, infection control, and other prevention practices into other health programs such as clinics for antenatal care, family planning, prevention of mother-to-child HIV transmission, other maternal and child health programs, and drug treatment programs.

5. *Intensified treatment with ART* means providing early ART to all coinfected PLHIV regardless of their HIV disease stage.[30] First, as noted earlier, early ART results in a mortality reduction of greater than 50 percent among PLHIV already on treatment for active TB disease.[31] Second, widespread use of ART has been shown to significantly reduce the frequency of new TB disease among PLHIV.[32]

---

[26] It is possible that IPT's preventive effect in HIV-infected people may be limited to the period during which patients are taking the drug, at least in part because much of the risk of TB disease in PLHIV over the longer term is derived from *new* TB infections.
[27] Ankur Gupta et al., "Prevalent and Incident Tuberculosis Are Independent Risk Factors for Mortality among Patients Accessing Antiretroviral Therapy in South Africa," *PLOS ONE* 8, no. 2 (2013): 1–8. http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0055824&representation=PDF.
[28] Salome Charalambous et al., "Association of isoniazid preventive therapy with lower early mortality in individuals on anti-retroviral therapy in a workplace programme," *AIDS* 24, Supplement 5 (2010): S-5–S-13.
[29] USAID, CDC, PEPFAR, NIAID, "Accelerating Impact: Expanding Access to Care," 2012, 22, http://www.usaid.gov/sites/default/files/documents/1864/tb_report2013.pdf.
[30] ART should begin generally within eight weeks of starting TB treatment. For PLHIV with more severe AIDS-related immunosuppression, ART should be provided within the first two weeks of starting TB treatment.
[31] S. S. Abdool Karim et al., "Timing of initiation of antiretroviral drugs during tuberculosis therapy," *New England Journal of Medicine* 362, no. 8 (February 25, 2010): 697–706.
[32] Stephen D. Lawn et al., "Antiretrovirals and Isoniazid," *Lancet Infect Disease* 10 (July 2010): 489–98.

Finally, another recent South African study demonstrated the frequency and adverse disease control impacts of social constraints such as stigma and poverty that can obstruct early diagnosis, care, and treatment of both HIV and TB disease.[33]

How the U.S. Government Is Tackling Global TB/HIV Coinfection

Current U.S. global policy on TB, including TB among PLHIV, has at its core the Lantos-Hyde legislation of 2008[34] that, among other things, called for the development of a U.S. government TB strategy. The resulting 2010 U.S. Global TB strategy[35] identified the Office of the Global AIDS Coordinator (OGAC) as the lead agency—through PEPFAR—for the U.S. government response to global TB/HIV infection. The strategy also reaffirmed U.S. support for the objectives of the Global Plan to Stop TB (including implementation of the "Three I's"), and called for expanded U.S. coverage of TB/HIV interventions, including implementation of TB/HIV activities in up to 25 additional countries.

U.S. agencies are also supporting the implementation of WHO's most recent TB/HIV policy,[36] which is based on 12 recommended collaborative TB/HIV activities that include the "three I's" (Box 2).

In December 2012, U.S. government engagement in global control of HIV-related TB was further clarified and strengthened with the release of the "PEPFAR Blueprint: Creating an AIDS-free generation," a document that outlines the U.S. government's operational HIV/AIDS control strategy.[37] An effort to target HIV-related TB, thereby reducing comorbidity and TB-related mortality, was listed first among the Blueprint's seven high-priority "Smart Investments," signaling the importance that PEPFAR attaches to appropriately emphasizing TB prevention, diagnosis, and care.

Five "Action Steps" outlined in the Blueprint document spell out a general technical approach for how the U.S. government will work in partnership with national TB and HIV programs to address TB/HIV coinfection. For example, the Blueprint calls for early diagnosis and treatment of TB among PLHIV and for PEPFAR programs to promote immediate access to ART for "all persons living with HIV who are diagnosed with TB and on appropriate treatment," regardless of their disease stage.[38]

---

[33] A. Daftary and N. Padayatcha, "Social Constraints to TB/HIV Healthcare: Accounts from Coinfected Patients in South Africa," *AIDS Care* 24 (December 2012): 1480–86. The list of social constraints discussed in that study included, for example, patient income, eligibility for social assistance and for ART, disease-related stigma, fears around illness disclosure, and disparate gender roles.
[34] Tom Lantos and Henry J. Hyde United States Global Leadership against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008, Section 302, http://www.gpo.gov/fdsys/pkg/PLAW-110publ293/html/PLAW-110publ293.htm.
[35] USAID, "Lantos-Hyde United States Government Tuberculosis Strategy."
[36] WHO, *WHO policy on collaborative TB/HIV activities*.
[37] Office of the Global AIDS Coordinator, "PEPFAR Blueprint: Creating an AIDS-free Generation," November 2012, http://www.pepfar.gov/documents/organization/201386.pdf.
[38] The CD4 count is a blood test-based measure of immune system functioning commonly used as an indicator for determining when to initiate ART in PLHIV.

Box 2. Collaborative TB/HIV Activities Recommended by the World Health Organization

A. Establish and strengthen the mechanisms for delivering integrated TB and HIV services

1. Set up and strengthen a coordinating body for collaborative TB/HIV activities functional at all levels;
2. 2. Determine HIV prevalence among TB patients and TB prevalence among people living with HIV;
3. Carry out joint TB/HIV planning to integrate the delivery of TB and HIV services;
4. Monitor and evaluate collaborative TB/HIV activities.

B. Reduce the burden of TB in PLHIV and initiate early antiretroviral therapy (the "Three I's")

1. Intensify TB case-finding and ensure high-quality anti-TB treatment;
2. Initiate TB prevention with isoniazid preventive therapy and early antiretroviral therapy;
3. Ensure control of TB Infection in health-care facilities and congregate settings.

C. Reduce the burden of HIV in patients with presumptive and diagnosed TB

1. Provide HIV testing and counseling to patients with presumptive and diagnosed TB;
2. Provide HIV prevention interventions for patients with presumptive and diagnosed TB;
3. Provide cotrimoxazole preventive therapy for TB patients living with HIV;
4. Ensure HIV prevention interventions, treatment, and care for TB patients living with HIV;
5. Provide antiretroviral therapy for TB patients living with HIV.

Adapted from: WHO, *WHO policy on collaborative TB/HIV activities: Guidelines for national programmes and other stakeholders* (Geneva: WHO, 2012), http://whqlibdoc.who.int/publications/2012/9789241503006_eng.pdf?ua=1.

The PEPFAR Stewardship and Oversight Act of 2013, signed into law on December 2, 2013, reaffirmed for an additional five years (i.e., 2014–2018) the U.S. government's serious commitment to tackling the global problem of TB in PLHIV.[39] With an increased focus on measurement and oversight, the new legislation includes annual reporting requirements on specific indicators of efforts to address coinfections and comorbidities of HIV/AIDS, including the number and proportion of PLHIV who started tuberculosis treatment and the number and percentage of eligible PLHIV starting IPT.

Several U.S. Government Agencies Are Responding to Global TB among PLHIV

OGAC and PEPFAR, with collaboration from USAID, the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH), lead the funding and implementation of the U.S. government's global TB/HIV activities.[40]

USAID is considered the lead agency for international TB control, in charge of overall U.S. efforts on global TB, including country-level support to national TB programs for

[39] PEPFAR Stewardship and Oversight Act of 2013, Public Law 113-56, December 2, 2014, http://www.gpo.gov/fdsys/pkg/PLAW-113publ56/pdf/PLAW-113publ56.pdf.
[40] UNAID, "Lantos-Hyde United States Government Tuberculosis Strategy."

the scaling up of aspects of the Stop TB Strategy.[41] Several U.S. agencies are working on implementation of infection control strategies to prevent new TB infections among PLHIV.[42]

CDC, together with PEPFAR and USAID, supports national HIV/AIDS programs and national TB programs in the planning, implementation, and evaluation of clinical services for HIV/AIDS and TB prevention, diagnosis, care, and treatment. CDC staff provides technical expertise and conduct implementation research in various countries on innovative service delivery options. NIH provides leadership on the design and funding of research.

PEPFAR in the Lead

> "Indeed, addressing TB should be a core function of HIV services."[43]

While PEPFAR is explicitly intended to help control HIV/AIDS (and has done a stellar job of extending the lives of PLHIV in selected countries by facilitating access to ART), PEPFAR investments also help address TB and a range of other diseases and public health challenges.

A formal evaluation of PEPFAR,[44] conducted by the Institute of Medicine (IOM) in 2011–2012, addressed the "Screening, Diagnosis, and Treatment of Tuberculosis."

Among PEPFAR's programmatic, policy, and systems successes, the IOM committee noted its:

- consistent emphasis on TB issues in the guidance documents that direct the development of the annual country operating plans (COPs) and country team budgets;
- strong technical assistance and budget support for the development and rollout of the new Xpert TB diagnostic test kits;
- increased TB treatment access and implementation for PLHIV;
- increased HIV testing access and referral completion for patients with active TB;
- support for efforts to link national TB and HIV/AIDS programs, including integration of TB and HIV activities;
- support for implementation of IPT programs;

[41] A more complete description of USAID's extensive global TB control activities can be found in the overview paper in this series: J. Stephen Morrison and Phillip Nieburg, "Strategic U.S. Leadership—Essential to Address the Global Tuberculosis Pandemic," CSIS, June 2014, http://www.csis.org/tuberculosis.
[42] See, for example, USAID, "FAST: A Tuberculosis Infection Control Strategy," March 2013, https://drtbnetwork.org/sites/default/files/FAST%20May%202013%20Booklet.pdf.
[43] K. F. Laserson and C. D. Wells, "Reaching the Targets for tuberculosis Control: the Impact of HIV," *Bulletin of the World Health Organization* 85, no. 5 (May 2007): 377–81.
[44] Institute of Medicine, *Evaluation of PEPFAR* (Washington, DC: National Academies Press, 2013), 266–72.

- support for development of national guidelines and tools; and
- support for decentralization of comprehensive HIV services that often includes TB services.

Among PEPFAR's ongoing challenges,[45] the IOM report highlighted:

- ongoing competition within many countries for funding between TB and HIV programs;
- the continued separation of TB and HIV systems for monitoring and evaluation;
- a failure to meet TB screening targets for PLHIV (versus exceeding the targets for numbers of PLHIV enrolled in clinical care); and
- a parallel failure to meet TB care targets for PLHIV (versus successfully meeting ART targets for those same people).

Another recent publication indicated that proportional reductions in TB incidence and TB mortality over PEPFAR's first 11 years were significantly greater in twelve sub-Saharan PEPFAR "focus countries" than in neighboring "non-PEPFAR" countries.[46] These latter results are both a tribute to PEPFAR, including the enormous impact of PEPFAR-facilitated ART in reducing TB-related mortality, and a strong reminder of PEPFAR's indispensable role in the U.S. government's global TB strategies and programs.

PEPFAR has also moved aggressively to increase HIV testing and counseling among known TB patients in order to expand access to early ART among those patients who are also PLHIV. PEPFAR resources have been provided to expand availability of Xpert MTB/RIF technology to identify PLHIV with TB disease and to indicate which of them are most likely to be infected with drug-resistant TB. PEPFAR resources have also been used to facilitate the inclusion of HIV data and TB drug resistance data into national TB surveillance systems.

The PEPFAR resources explicitly allocated to TB/HIV control activities increased by over 700 percent from FY 2005 ($19 million) to FY 2009 ($160 million).[47] However, that specific TB/HIV allocation, currently representing only about 3 percent of PEPFAR's overall budget, has not increased since FY 2009.[48]

---

[45] Because the data used to draw the conclusions reached in the IOM report are now several years out of date, progress is likely to have occurred in many—or all—PEPFAR program areas that were of concern to the IOM committee. Parenthetically, TB was addressed in the "Treatment and Care" chapter of the IOM report but was not addressed in its "Prevention" chapter.

[46] Viviane D. Lima et al., "Potential Impact of the US President's Emergency Plan for AIDS Relief on the Tuberculosis/HIV Coepidemic in Selected Sub-Saharan African Countries," *Journal of Infectious Diseases* 208, no. 12 (August 2, 2013): 2075–84.

[47] Office of the Global AIDS Coordinator, "PEPFAR Blueprint," 27.

[48] Beyond the specific activities funded by PEPFAR's $160 million TB/HIV allocation, it is likely that many other aspects of PEPFAR's program support—such as HIV testing, program monitoring, access to ART, supply chain management—have indirectly benefited ongoing efforts to address TB/HIV coinfection.

Other Organizations with Major Roles in Control of Global TB/HIV Coinfection[49]

The World Health Organization (WHO)

WHO produced an initial set of interim recommendation for managing TB/HIV coinfection issues in 2004 and updated them in 2012.[50] Known collectively as the collaborative TB/HIV activities, these recommendations are centered on three specific goals: (1) establishing and strengthening delivery of integrated HIV/AIDS and TB program services; (2) reducing the burden of TB among PLHIV, which includes the *Three I's for HIV/TB* and early ART for TB prevention; and (3) reducing the burden of HIV in TB patients through provision of services for HIV prevention, HIV testing and counseling, and early ART and cotrimoxazole preventive therapy[51] for coinfected patients. WHO also ensures that global TB and TB/HIV data are harmonized across agencies and produces an annual comprehensive summary of those TB data,[52] the most recent edition of which lists the 41 countries that have high burdens of both TB and HIV. In addition, WHO provides technical support to national TB programs for scaling up the implementation and reporting of collaborative TB/HIV activities.

The Stop TB Partnership

Created in 2001, the Stop TB Partnership is hosted at WHO headquarters and shares with WHO the sponsorship of the current Global Plan to Stop TB 2011–2015.[53] One of the partnership's major goals is to increase resources available for TB control activities (and, by implication, for TB/HIV control activities). The partnership also includes a Global TB/HIV Working Group, currently chaired by ex- Global AIDS Coordinator Dr. Eric Goosby. WHO manages that working group's secretariat, and the group has been involved in the past in the updating of the Global Plan to Stop TB and in guiding the global advocacy for control of TB in PLHIV.

The Global Fund to Fight AIDS, Tuberculosis and Malaria

Because the Global Fund is the largest external funder of global TB control activities, its greatest impact in addressing TB/HIV coinfection is likely to be through incentivizing the collaboration of domestic TB and HIV program activities in countries

---

[49] A detailed review of the role of international organizations in global TB control activities can be found in a companion paper in this series: Nellie Bristol, "Toward a Well-oiled Machine: U.S. Government Engagement with Multilateral Organizations in Pursuit of Global TB Control," CSIS, June 2014, http://www.csis.org/tuberculosis.

[50] WHO, *WHO policy on collaborative TB/HIV activities*. In addition, the International Union Against Tuberculosis and Lung Disease has recently published a comprehensive guide on the same topic: Paula I. Fujiwara et al., *Implementing Collaborative TB-HIV Activities: A Programmatic Guide* (Paris: International Union Against Tuberculosis and Lung Disease, 2012), http://www.theunion.org/what-we-do/publications/technical/english/pub_tb-hivguide_eng_web-1.pdf.

[51] In the United States, the generic name for cotrimoxazole is trimethoprim-sulfamethoxazole. This drug combination has been shown to significantly reduce respiratory disease and overall mortality in HIV-infected children and adults, including those with coexisting TB disease.

[52] WHO, *Global Tuberculosis Report 2013*, Chapter 6: Addressing the coepidemics of TB and HIV. WHO also produces an annual global HIV report and provides technical support to UNAIDS for the latter's global reporting.

[53] Stop TB Partnership and WHO, *The Global Plan to Stop TB, 2011–2015*.

receiving future Global Fund grant awards. In the past, only about 1 percent of its AIDS grant funding and 3 percent of its TB grant funding was specifically directed at joint TB/HIV collaborative activities.[54] However, recent Global Fund guidance indicates to prospective grant applicants and proposal reviewers that, for countries with high burdens of both HIV and TB disease, the organization will require from this point forward joint in-country proposal planning by national TB and HIV programs (and country coordinating mechanisms[55]) and submission of unified national applications for TB and HIV control programs.[56]

Key Challenges

- Global integration and coordination are critical processes but not yet optimally implemented.

Given that TB and HIV/AIDS often affect the same individuals, it seems obvious that each disease must be prevented and controlled in the context of the other and that the programs working to control them must collaborate closely. The most recent data indicate ongoing progress in TB and HIV program coordination but many national programs to address these two diseases are still hampered by "stovepipe" mindsets. The recent step taken by the Global Fund to require unified (TB and HIV/AIDS) national grant applications is likely to help break down barriers. Strong encouragement by U.S. government agencies can only help accelerate those coordination and integration processes.[57]

One obstacle to greater program coordination may be that some clinicians and health policymakers have not been totally aware of the frequency, severity, and mortality potential of tuberculosis disease among PLHIV. For example, some may have been unaware of the multicountry autopsy study findings indicating that very large proportions of patients dying with AIDS have disseminated TB infections, some of which were unknown prior to death.[58] It may be that the increasing availability and use of Xpert MTB/RIF diagnostic testing technology, which can improve the odds of

[54] The Global Fund to Fight AIDS, Tuberculosis and Malaria, "Funding and Spending," http://www.theglobalfund.org/en/about/fundingspending/.
[55] "Country Coordinating Mechanisms are . . . country-level multi-stakeholder partnerships [that] develop and submit grant proposals to the Global Fund based on priority needs at the national level. After grant approval, they oversee progress during implementation. Country Coordinating Mechanisms include representatives from both the public and private sectors, including governments, multilateral or bilateral agencies, non-governmental organizations, academic institutions, private businesses and people living with the diseases." See The Global Fund, "Country Coordinating Mechanisms," http://www.theglobalfund.org/en/ccm/.
[56] The Global Fund, "Global Fund Board Decision: Submissions of Single Concept Notes for HIV and TB" (paper presented at ESA regional meeting on Global Fund single TB and HIV concept notes, February 17–19, 2014), http://www.who.int/tb/challenges/hiv/session_2a_global_fund_board_decision_single_concept_notes.pdf.
[57] PEPFAR, "Technical considerations provided by PEPFAR technical working groups for FY 2014 COPS and ROPS," October 2013, 185. See also WHO, *Global Tuberculosis Report 2013*, Chapter 6.
[58] Cox et al., "Autopsy Causes of Death in HIV-Positive Individuals in Sub-Saharan Africa and Correlation with Clinical Diagnoses"; and Havlir, "State of the HIV/TB Epidemic: Opportunities and Challenges."

correctly diagnosing TB disease in PLHIV, can also improve clinicians' and policymakers' awareness of the risks of TB in this group.[59]

- PEPFAR's influence on global HIV/AIDS is not yet matched by the intensity of its TB focus.

Because of PEPFAR's well-documented successes[60] and its global prominence in HIV/AIDS issues, it is viewed clearly as a global leader in HIV/AIDS control and, by implication, a leader on many issues related to TB among PLHIV. PEPFAR's programming and funding decisions regarding prevention and control of TB/HIV coinfections will continue to have a large influence over the U.S. role in the control of global TB and TB/HIV. To that point, the set of complex challenges involved in control of TB/HIV coinfection may need a still higher priority within PEPFAR activities. For example, although the screening for—and treatment of—TB disease is now a global standard of care for PLHIV, the most recent reported global rate/coverage of TB screening among PLHIV in HIV care was only 66 percent.[61]

- Insufficient funding and coordination.

The 2010 Lantos-Hyde TB Strategy was an important step toward a coherent U.S. government approach to global TB. However, most of the $8 billion that was intended for global TB programs during FY 2009–2013 was never appropriated, somewhat compromising the value of that guidance.

In addition, that strategy assigned USAID as the "lead agency for international TB control," while OGAC was named as "the lead for USG response to TB-HIV coinfection" through PEPFAR—a division of labor that includes a large overlap of programmatic needs and tools (e.g., TB screening and diagnostic testing, surveillance systems, national TB control program activities and priorities, ART coverage and priorities, program evaluations).[62] Although there may be some benefit to these overlapping responsibilities, some experts believe that a U.S. government-wide strategic vision that addresses coordination and allocation of TB and TB/HIV resources is needed at country levels and, presumably, at a central level as well.[63]

- Differing perspectives on the global importance of TB among PLHIV.

---

[59] Many active TB cases in PLHIV affect organs outside the lungs, and even those that do occur in the lungs can be difficult to diagnose with the usual sputum microscopy.
[60] Much of PEPFAR's success can probably be attributed to OGAC's strong leadership and coordination roles in the activities and funding streams of multiple agencies, both globally and at a country level. See, for example, Andrea A. Howard et al., "PEPFAR Support for the Scaling Up of Collaborative TB/HIV Activities," *Journal of Acquired Immune Deficiency Syndrome* 60, Supplement 3 (August 15, 2012): S136–S144.
[61] WHO, *Global Tuberculosis Report 2013*, 74. It is possible that TB screening in specific PEPFAR-supported programs is being done more often than the 66 percent global average but just not being well documented. However, there were no publically available data from which to conclude that.
[62] In a number of countries where PEPFAR and USAID both operate TB programs, the TB-related resources from these two funding sources are programmed jointly, a sign of both active and effective interagency cooperation and of the relative importance attached to TB among PLHIV.
[63] PEPFAR, "Technical considerations provided by PEPFAR technical working groups for FY 2014 COPS and ROPS," October 2013, 199.

There is little doubt about the importance of local epidemiologic data (i.e., "know your epidemic") in the planning of national and subnational TB and TB/HIV control programs. Beyond that, there are varying perspectives on the global importance of TB among PLHIV. One perspective seems to be that HIV is a major driver of the TB pandemic only in eastern and southern Africa and perhaps in parts of Eastern Europe, and the TB-affected populations in question are modest in proportion to the overall global TB-affected population. Computer modeling data suggest, for instance, that only 13 percent of new global TB patients in 2012 were HIV infected.[64]

However, other risk numbers are higher. Global TB case reporting data indicate that 20 percent of TB patients who were HIV-tested in that year were found to be HIV infected.[65] In addition, HIV-associated TB accounted for an estimated 25 percent of all TB deaths in 2012. In sub-Saharan Africa, where the bulk of PEPFAR's $50 billion has been invested, and where HIV is a predominant driver of TB's spread, 43 percent of new TB patients are also infected with HIV. Also in sub-Saharan Africa, women of reproductive age are disproportionally affected by HIV.[66] Probably as a consequence of that inequity, women who died from TB in 2012 were twice as likely to be HIV infected as men who died from TB.[67]

Several other factors raise the importance of HIV/AIDS in the U.S. calculus of its interests and its approach to global TB. First, although numbers of *new* HIV infections are declining in many places, overall numbers of PLHIV continue to increase globally because many more PLHIV are receiving life-extending antiretroviral treatment (ART). The excess TB risk of these PLHIV appears to continue even while they are on ART.[68]

Finally, when considered in the context of USAID's annual TB budget of $230–238 million, PEPFAR's TB/HIV allocation of up to $160 million annually since 2009 has represented about 40 percent of the U.S. government's total resources directed bilaterally at programs global TB control.[69]

Recommendations

- Reverse the funding shortfall.

In recent years, PEPFAR has allocated up to $160 million annually to control of TB/HIV coinfection. In addition, the Global Fund, largely supported by the United States, is beginning to more specifically focus resources on TB/HIV coinfection challenges. Because it seems clear that that PEPFAR's long-term success in saving lives depends on

[64] WHO, *Global Tuberculosis Report 2013*, 9, table 2.1.
[65] Ibid., 70, table 6.1. In 2012, only 46 percent of reported TB patients had a documented HIV test result.
[66] Global Coalition on Women and AIDS, "Tackling TB and HIV in Women: An Urgent Agenda," July 2012, http://www.womenandaids.net/CMSPages/GetFile.aspx?guid=aaee44f9-9a9d-4366-9ee4-89e4775cc798&disposition=inline.
[67] WHO, *Global Tuberculosis Report 2013*, 9 and 12. These calculations were made from several estimates presented in table 2.1 and box 2.2.
[68] Gupta et al., "Prevalent and Incident Tuberculosis Are Independent Risk Factors for Mortality among Patients Accessing Anti-retroviral Therapy in South Africa."
[69] For example, in FY 2013, a year in which USAID's TB budget was $236 million, PEPFAR's $160 million for TB/HIV represented approximately 40 percent of the combined $396 million of U.S. bilateral TB-related funding.

control of TB infection in PLHIV and thus on effective control of global TB. Making sufficient resources available to allow greater implementation of the TB-related recommendations specified in legislation and the resulting global TB strategies of the United States could have an important life-saving impact on PLHIV who also have TB disease or are at risk of TB infection.

In addition to meeting USAID's obvious need for a more robust TB budget to help continue to address both drug-sensitive and drug-resistant TB globally, the United States should increase significantly the proportional TB-related allocations of PEPFAR from its current 3 percent. (We are aware that increasing the PEPFAR funds allocated to TB and TB/HIV activities could become easier if the overall PEPFAR budget rises above current levels. But, even at current levels, it is puzzling that only 3 percent of PEPFAR resources are allocated to TB/HIV, an essentially preventable disease complication responsible for at least 20 percent of all AIDS deaths.)

- Underscore the lifesaving value of integrating TB and HIV/AIDS programs.

Future PEPFAR funding announcements, COP guidance, COPs themselves, and discussions with national program staff should strongly encourage, and, where appropriate, incentivize the integration (or coordination) of programs with the potential to prevent TB among PLHIV, identify and treat coinfected people, provide IPT, and control TB transmission to PLHIV. Wherever possible, TB control activities should be further integrated with other health programs, e.g., family planning, prevention of mother-to-child [HIV] transmission, nutrition, and other maternal, child, and newborn health issues.

- Intensify TB screening of PLHIV and HIV testing of TB patients, and ensure their appropriate referral.

U.S. officials in OGAC, Congress, and successive administrations have well understood the importance of antiretroviral treatment (ART) in global efforts to reduce mortality in, and otherwise control, both HIV/AIDS and TB. To further reduce the tens of thousands of preventable TB-related AIDS deaths, future U.S. government legislation and program implementation activities should reemphasize *prevention* of TB among PLHIV through aggressive application of the "Three I's."

OGAC should further enhance the success of ongoing PEPFAR prevention efforts against TB/HIV coinfection by requiring that comprehensive data be submitted on coverage and follow-up of the recommended TB screening of PLHIV in PEPFAR-supported programs that provide ART to those same PLHIV.

- Capitalize on existing PEPFAR work toward the control of TB and TB/HIV.

In the absence of an official PEPFAR guidance document on TB among PLHIV,[70] OGAC should also explore ways to promote more widely the concise recommendations and thoughtful suggestions on magnitude and control of TB/HIV that already exist in the

[70] PEPFAR does in fact have an excellent set of recommendations for TB screening of PLHIV, but it applies only to children and pregnant women. See PEPFAR, "PMTCT/Pediatric HIV Technical Working Group Recommendations for Integration of Tuberculosis Screening into PMTCT/Pediatric HIV Programs," July 2012, http://www.pepfar.gov/documents/organization/194952.pdf.

Technical Considerations documents produced annually by PEPFAR's Technical Working Group(s). However, most of these recommendations are unaccountably labeled as "not official guidance," a label that would seem to undercut their validity in the eyes of others. As an initial step, the "not official" disclaimer should be removed.

- Minimize any potential adverse impact of PEPFAR's transition to country ownership.

We are aware that the coming PEPFAR transition toward country ownership is of a magnitude that has not been attempted before. Because of this, it may be a long process in many countries. OGAC and PEPFAR country teams should anticipate and monitor the challenges that the transition may inadvertently pose to control of TB/HIV coinfection.

CSIS | CENTER FOR STRATEGIC & INTERNATIONAL STUDIES

1616 Rhode Island Avenue NW | Washington, DC 20036
t. (202) 887-0200 | f. (202) 775-3199 | www.csis.org

Cover photo: https://www.flickr.com/photos/64153924@N08/8634251644/in/photolist-e9YNcE-hjBU1w-7Nggwq-hjCYsK-axvvsb-hfE9fA-8gTRWk-aoC3Jv-dapLqb-dapK8g-f5JV1E-f5uCZp-f5JW3h-f5uD8c-f5uDjt-9zfgxN-hmgVZi-hmfKfC-hmeH4z-hmeP3D-9yyhfc-hm1fQ7-f5uECH-f5JV9E-f5uDv6-f5JUXJ-8BxKRb-.