

# Synergistic Pandemics: Confronting the Global HIV and Tuberculosis Epidemics

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This supplement was envisioned to summarize the critical issues related to the 2 most deadly infectious diseases worldwide: human immunodeficiency virus (HIV) infection and AIDS and tuberculosis (TB). Together, these infections—1 viral and 1 bacterial, 1 recently emergent and 1 ancient—kill almost 4 million persons every year, most of whom live in developing nations. In tandem, HIV infection and TB create a deadly synergy. TB is the leading cause of death among persons with HIV infection, and areas with a high prevalence of HIV infection have had dramatic increases in the incidence of TB disease.

The US government has played a leadership role in addressing the HIV and TB pandemics, most recently through the enactment of the Tom Lantos and Henry J. Hyde United States Global Leadership Against HIV/AIDS, Tuberculosis and Malaria Authorization Act of 2008, which authorized \$48 billion over 5 years to combat these deadly infectious diseases in developing nations. We hope that this supplement of scientific review articles focused on HIV infection prevention, TB, and HIV and TB coinfection will serve as a resource for policy makers, HIV and TB program

implementers, and advocates as they develop and deploy the US response to these twin scourges.

Nearly 3 decades after HIV first emerged, major advances in the scientific understanding of HIV infection and the rapid development of first- and second-line antiretroviral therapy (ART) have transformed HIV infection and AIDS from a death sentence to a chronic, manageable illness. In recent years, almost 4 million people in resource-constrained settings received access to life-saving drugs for HIV infection, and many are living active, productive lives as a result.

However, the AIDS pandemic continues to present unprecedented public health challenges in an era of increasing global interconnectedness. HIV infection and AIDS killed ~2 million persons in 2008, including more than a quarter million children. An estimated 33 million persons were living with HIV infection at the end of 2008, and less than half of those who urgently needed ART to prevent serious illness or death were actually receiving it. Despite increasing evidence that earlier initiation of ART may prevent long-term sequelae of chronic immunosuppression, the gap between persons who need medication and those who are actually receiving ART could continue to increase in under-resourced settings. Sixty-seven percent of all estimated HIV infections occur in sub-Saharan Africa, with 8 countries in that region reporting

prevalence rates of adult HIV infection of  $\geq 15\%$ .

Furthermore, the successes in HIV treatment have not been matched by similar gains in prevention. At the 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention in July 2009, Ronald Gray, MD, of John Hopkins' Bloomberg School of Public Health, reported that, of the 29 completed biomedical prevention trials in the past 2 decades, only 4 have shown efficacy in reducing the incidence of HIV infection; 3 of the trials involved male circumcision, which was only shown to be protective for heterosexual male individuals [1]. Most preventive vaccine and topical microbicide trials have not had promising results. Data from RV-144, a Thai study [2] of a combination anti-HIV vaccine, suggested a 30% decrease in the rate of new HIV infection. This level of protection is not sufficiently effective to arrest the spread of HIV infection in heavily impacted communities but suggests that ultimate control of new infections through biomedical interventions may be feasible. Proof-of-concept trials will take many more years to complete, however, during which there will be millions of new HIV infections.

Meanwhile, ideologically driven prevention policies, such as abstinence-only programs and the prohibition of syringe-exchange programs by several governments (including the former administration in the United States), have seriously

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hampered efforts to mount effective evidence-based educational campaigns that could stem the tide of new infections. As a result, the epidemic's spread has significantly outpaced the steps toward effective prevention and treatment. For every person initiating ART in 2007, there were nearly 3 new HIV infections; in 2007, 2.7 million individuals became newly infected with the virus.

## HIV INFECTION PREVENTION

The HIV infection prevention section of this supplement begins with an overview of the global HIV epidemic and the public health and clinical responses, with discussions on the challenges that remain, including sustaining political and financial commitments, building health care infrastructure in resource-constrained environments, and ensuring that human rights are respected. Bassett and Walensky [3] review the state of HIV screening, with a focus on health care settings, the backbone of HIV prevention and treatment interventions. Grant [4] provides an update on critical studies evaluating the efficacy of ART for prevention (orally and topically) before and after a possible sexual transmission event, and Cohen and Gay [5] offer a critical review of the data that support the belief that ART has major potential as a prevention strategy. DeGruttola et al [6] describe the potential for treatment as prevention from a community perspective and present the argument that testing and treating all newly identified HIV-infected persons could arrest the spread of the epidemic. Four important review articles by Beyrer [7], Vlahov et al [8], Abdool Karim et al [9], and Mofenson [10] address critical subpopulations that each require tailored prevention interventions to have an impact in the global epidemic: men who have sex with men, injection drug users, women, and infants. An article by Vermund et al [11] on the role of prevention in combating the HIV epidemic in the United States describes the complex and unrelenting HIV epidemic in the United States that requires re-

sources, vigilance, and targeted, evidence-based strategies.

## TB

At present, one-third of the worldwide population is infected with *Mycobacterium tuberculosis*; there were an estimated 13.7 million prevalent cases of TB disease in 2007, according to the World Health Organization. Approximately 9.3 million new TB cases were detected in 2007, and nearly 1.8 million persons died of the disease. An estimated 5% of all cases of active TB are multidrug resistant, and <3% of persons with multidrug-resistant TB receive appropriate treatment. Among infectious diseases, TB is the leading cause of death among women and is 1 of the top 10 causes of death among children worldwide.

These are sobering statistics for a disease for which curative antibiotics have been available for 50 years. Weak TB control programs, lengthy treatment regimens with toxic medications, limited attention to infection control, inadequate investments in research and development, and the impact of the HIV epidemic have all served to make *M. tuberculosis* a tenacious and increasing threat to the public health in many regions of the world. Although drug-resistant TB continues to spread across the world, the last truly novel TB drug was developed >4 decades ago, and the most frequently used TB diagnostic, sputum microscopy, is more than a century old and fails to detect *M. tuberculosis* in half of those with active TB disease and performs even more poorly in those coinfecting with HIV.

The supplement section on TB begins with a review by Jassal and Bishai [12] on the epidemiology of TB and the challenges of TB elimination, including a dearth of resources; inadequate attention to socioeconomic determinants of TB vulnerability, such as malnutrition and inability to pay for TB services; inadequate attention to infection control in health care and community settings; and failure to scale-up diagnosis and care of the HIV-TB-

coinfecting population. Burman [13] offers a review of current TB therapeutics and the articulated goal for improved TB treatment strategies and provides a glimmer of hope by highlighting new agents currently in clinical development. Dorman [14] presents the status inadequacies of current tools for TB diagnosis and describes promising new technologies and their implementation challenges. Beresford and Sadoff [15] review progress toward developing an effective TB vaccine and highlight the advocacy that will be needed to ensure that resources are available to develop, manufacture, and distribute it. Swaminathan and Rekha [16] outline the special challenges presented by pediatric TB, a major cause of death among children worldwide, and the urgent need for enhanced research and development to formulate shorter and more effective treatment regimens for children. Cegielski [17] completes the TB section with a commentary on multidrug-resistant TB and offers a historical perspective on the missteps by governments, international health agencies, and policy makers that have contributed to another serious resurgence of deadly drug-resistant TB.

## HIV AND TB COINFECTION

When a patient is infected with both *M. tuberculosis* and HIV or AIDS, the 2 pathogens interact synergistically, speeding the progression of illness and increasing the likelihood of death. The presence of HIV makes a person more vulnerable to developing TB disease, and having TB disease accelerates HIV disease progression. TB is the most common opportunistic infection among persons infected with HIV, and HIV-infected patients with TB are at high risk of death.

In 2007, 1.37 million people infected with HIV were estimated to be coinfecting with TB, according to the World Health Organization, and 1 of 4 deaths from TB is now HIV related. In regions with a high prevalence of HIV infection, the AIDS epidemic has stoked an increase in the number of cases of TB, including those caused

by drug-resistant strains of *M. tuberculosis*. Health care systems in most developing countries have been under-resourced and poorly managed for decades. Individuals coinfecting with TB and HIV or AIDS personify the difficulties that such weak health systems pose. Although data are lacking on how long persons in developing countries wait before going to a TB diagnostic center (which are frequently centrally located and not at the village level), after an individual is seen at the center, the lag between TB diagnosis and treatment can take up to 6 weeks, delaying access to early treatment. TB, if unchecked in settings with a high prevalence of HIV infection, threatens to undermine the progress made in the number of lives saved as a result of access to HIV therapy.

The discussion in this supplement about HIV and TB coinfection begins with a review article by Getahun et al [18] that describes the epidemiology of HIV-associated TB and the progress, to date, in implementing the key interventions identified in the World Health Organization Policy on Collaborative TB/HIV Activities. Granich et al [19] argue for marshalling comprehensive, evidence-based HIV infection and TB prevention interventions, with a particular focus on isoniazid preventive treatment for persons with HIV infection. Bekker and Wood [20] analyze the drivers of an explosive HIV and TB coepidemic in a township in Cape Town, South Africa, and argue for new community-based interventions to reduce the prevalence of TB in this community. Sterling and Chaisson [21] provide the latest information and evidence about treatment of TB in HIV-infected individuals, including a discussion on when to start ART after TB treatment has been initiated and information about drug-drug interactions. Sheno et al [22] provide a review of respiratory infection control in resource-poor settings and its challenges. Chamie et al [23] outline an enhanced and refocused research agenda highlighting improved point-of-care diagnostics, treatment, and prevention of HIV infection

throughout the course of HIV infection, drug-resistant TB, and pediatric TB, as well as optimal approaches to TB and HIV program integration. Howard and El-Sadr [24] review lessons learned in responding to HIV and TB coinfection in sub-Saharan Africa. Coggin et al [25] from the Office of the US Global AIDS Coordinator report on the role and activities of the President's Emergency Plan for AIDS Relief program in responding to HIV-TB coinfection, including relevant cross-cutting issues, such as human resources and laboratory strengthening.

The final article in this supplement is an activist perspective on the US response to global HIV infection, TB, and HIV-TB coinfection by Mark Harrington [26], executive director of the Treatment Action Group, who was one of the founders of AIDS Coalition to Unleash Power (ACT-UP), which put in a great effort to promote early access to life-saving ART. His analysis is a call to action that reminds us how political action has informed and will continue to inform the US government's research and programmatic response to the deadly twin pandemics of HIV infection and TB.

This supplement is a project of the Center for Global Health Policy, an organization of physicians and scientists dedicated to promoting the effective use of US funding for addressing the global HIV and AIDS and TB epidemics. The Center, created in October 2008 by the Infectious Diseases Society of America (IDSA) and the HIV Medicine Association (HIVMA), was established in response to the growing threat of HIV infection and AIDS and TB. The Center's mission is to ensure that policy makers, federal agencies, nongovernmental organizations, and the media have access to solid, evidence-based input and guidance from IDSA-HIVMA physician scientists and other professional colleagues from both developed and developing countries. The Center disseminates reliable, comprehensive scientific information about HIV infection and TB through publications, such as this supplement, is-

sue briefs, project profiles, a blog, and meetings and interviews with US policy makers, members of Congress, and journalists. In addition, the Center organizes visits by US policy makers to the research and program sites of IDSA-HIVMA members, both in the United States and in developing countries. In addition, the Center brings scientists from developing nations to the United States so that they can describe to US officials the reality of maintaining the worldwide progress against HIV infection and TB. The Web site is <http://www.idsaglobalhealth.org>, and our blog can be found at <http://sciences-peaks.wordpress.com>.

The IDSA is a professional society representing >8600 physicians and scientists who specialize in infectious diseases. The HIVMA is the professional home for >3600 physicians, scientists, and other health care professionals dedicated to the field of HIV infection and AIDS. Nested within the IDSA, the HIVMA promotes quality in HIV care and advocates policies that ensure a comprehensive and humane response to the AIDS pandemic, informed by science and social justice. The IDSA, the HIVMA, and the Center for Global Health Policy are all based in Arlington, Virginia.

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## References

1. Gray RH. Biomedical prevention including microbicides, vaccines, circumcision and PrEP. In: Program and abstracts of the 5th IAS Conference on HIV Pathogenesis and Treatment (Cape Town). 2009. Abstract TUPL101.
2. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 2009; 361:2209–2220.

3. Bassett IV, Walensky RP. Integrating HIV screening into routine health care in resource-limited settings. *Clin Infect Dis* **2010**; 50(Suppl 3):S77–S84 (in this supplement).
4. Grant RM. Antiretroviral agents used by HIV-uninfected persons for prevention: pre- and postexposure prophylaxis. *Clin Infect Dis* **2010**; 50(Suppl 3):S96–S101 (in this supplement).
5. Cohen MS, Gay CL. Treatment to prevent transmission of HIV-1. *Clin Infect Dis* **2010**; 50(Suppl 3):S85–S95 (in this supplement).
6. DeGruttola V, Smith DM, Little SJ, Miller V. Developing and evaluating comprehensive HIV infection control strategies: issues and challenges. *Clin Infect Dis* **2010**; 50(Suppl 3):S102–S107 (in this supplement).
7. Beyrer CB. Global prevention of HIV infection for neglected populations: men who have sex with men. *Clin Infect Dis* **2010**; 50(Suppl 3):S108–S113 (in this supplement).
8. Vlahov D, Robertson AM, Strathdee SA. Prevention of HIV infection among injection drug users in resource-limited settings. *Clin Infect Dis* **2010**; 50(Suppl 3):S114–S121 (in this supplement).
9. Abdool Karim Q, Sibeko S, Baxter C. Preventing HIV infection in women: a global health imperative. *Clin Infect Dis* **2010**; 50(Suppl 3):S122–S129 (in this supplement).
10. Mofenson LM. Prevention in neglected subpopulations: prevention of mother-to-child transmission of HIV infection. *Clin Infect Dis* **2010**; 50(Suppl 3):S130–S148 (in this supplement).
11. Vermund SH, Hodder SL, Justman JE, et al. Addressing research priorities for prevention of HIV infection in the United States. *Clin Infect Dis* **2010**; 50(Suppl 3):S149–S155 (in this supplement).
12. Jassal MS, Bishai WR. Epidemiology and challenges to the elimination of global tuberculosis. *Clin Infect Dis* **2010**; 50(Suppl 3):S156–S164 (in this supplement).
13. Burman WJ. Rip Van Winkle wakes up: drug development of tuberculosis treatment in the 21st century. *Clin Infect Dis* **2010**; 50(Suppl 3):S165–S172 (in this supplement).
14. Dorman SE. New diagnostic tests for tuberculosis: bench, bedside, and beyond. *Clin Infect Dis* **2010**; 50(Suppl 3):S173–S177 (in this supplement).
15. Beresford B, Sadoff JC. Update on research and development pipeline: tuberculosis vaccines. *Clin Infect Dis* **2010**; 50(Suppl 3):S178–S183 (in this supplement).
16. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. *Clin Infect Dis* **2010**; 50(Suppl 3):S184–S194 (in this supplement).
17. Cegielski JP. Extensively drug-resistant tuberculosis: there must be some kind of way out of here. *Clin Infect Dis* **2010**; 50(Suppl 3):S195–S200 (in this supplement).
18. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection-associated tuberculosis: the epidemiology and the response. *Clin Infect Dis* **2010**; 50(Suppl 3):S201–S207 (in this supplement).
19. Granich R, Akolo C, Gunneberg C, Getahun H, Williams P, Williams B. Prevention of tuberculosis in people living with HIV. *Clin Infect Dis* **2010**; 50(Suppl 3):S215–S222 (in this supplement).
20. Bekker L-G, Wood R. The changing natural history of tuberculosis and HIV coinfection in an urban area of hyperendemicity. *Clin Infect Dis* **2010**; 50(Suppl 3):S208–S214 (in this supplement).
21. Sterling TR, Chaisson RE. HIV infection-related tuberculosis: clinical manifestations and treatment. *Clin Infect Dis* **2010**; 50(Suppl 3):S223–S230 (in this supplement).
22. Shenoï SV, Escombe AR, Friedland G. Transmission of drug-susceptible and drug-resistant tuberculosis and the critical importance of airborne infection control in the era of HIV infection and highly active antiretroviral therapy rollouts. *Clin Infect Dis* **2010**; 50(Suppl 3):S231–S237 (in this supplement).
23. Chamie G, Luetkemeyer A, Charlebois E, Havlir DV. Tuberculosis as part of the natural history of HIV infection in developing countries. *Clin Infect Dis* **2010**; 50(Suppl 3):S245–S254 (in this supplement).
24. Howard AA, El-Sadr WM. Integration of tuberculosis and HIV services in sub-Saharan Africa: lessons learned. *Clin Infect Dis* **2010**; 50(Suppl 3):S238–S244 (in this supplement).
25. Coggin WL, Ryan CA, Holmes CB. Role of the US President's Emergency Plan for AIDS Relief in responding to tuberculosis and HIV coinfection. *Clin Infect Dis* **2010**; 50(Suppl 3):S255–S259 (in this supplement).
26. Harrington M. From HIV infection to tuberculosis and back again: a tale of activism in 2 pandemics. *Clin Infect Dis* **2010**; 50(Suppl 3):S260–S266 (in this supplement).